

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number
WO 02/055079 A2

(51) International Patent Classification⁷: **A61K 31/44**,
31/495, 31/50, 31/52, 31/53, 31/519, 31/517, 31/47, A61P
31/18, C07D 215/12, 215/16, 215/38, 237/26, 237/28,
239/72, 241/36, 251/00, 257/08, 401/02, 403/00, 471/00,
487/00

D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126
East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(21) International Application Number: PCT/US01/42565

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW.

(22) International Filing Date: 9 October 2001 (09.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/239,679 12 October 2000 (12.10.2000) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).

(71) Applicant (*for all designated States except US*): **MERCK
& CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway,
NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **ANTHONY,
Neville, J.** [GB/US]; 126 East Lincoln Avenue, Rahway,
NJ 07065-0907 (US). **GOMEZ, Robert, P.** [US/US];
126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
BENNETT, Jennifer, J. [US/US]; 126 East Lincoln
Avenue, Rahway, NJ 07065-0907 (US). **YOUNG, Steven,**

Published:

— *without international search report and to be republished
upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: AZA-AND POLYAZA-NAPHTHALENYL CARBOXAMIDES USEFUL AS HIV INTEGRASE INHIBITORS

(57) Abstract: Aza- and polyaza-naphthalenyl carboxamide derivatives including certain quinoline carboxamide and naphthyridine carboxamide derivatives are described as inhibitors of HIV integrase and inhibitors of HIV replication. These compounds are useful in the prevention or treatment of infection by HIV and the treatment of AIDS, as compounds or pharmaceutically acceptable salts, or as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of preventing, treating, or delaying the onset of AIDS and methods of preventing or treating infection by HIV are also described.

WO 02/055079 A2

AZA- AND POLYAZA-NAPHTHALENYL CARBOXAMIDES USEFUL AS HIV INTEGRASE INHIBITORS

5 FIELD OF THE INVENTION

The present invention is directed to aza- and polyaza-naphthalenyl carboxamides and pharmaceutically acceptable salts thereof, wherein the carboxamido nitrogen is part of a heterocyclic ring system. The present invention is also directed to the synthesis of the compounds and salts thereof and their use as
10 inhibitors of the HIV integrase enzyme. The compounds of the present invention include 7-carboxamido-8-hydroxy- 1,6-naphthyridines, quinolines, and quinoxalines in which the carboxamido nitrogen is part of a saturated or unsaturated heterocyclic ring which is optionally fused to a phenyl ring or a second heterocyclic ring. The compounds and pharmaceutically acceptable salts thereof of the present invention are
15 useful for preventing or treating infection by HIV and for treating AIDS.

References are made throughout this application to various published documents in order to more fully describe the state of the art to which this invention pertains. The disclosures of these references are hereby incorporated by reference in their entireties.

20

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and
25 degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the insertion by virally-encoded integrase of proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three
30 steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

5 Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)]. All three enzymes have been shown to be essential for the replication of HIV.

10 It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhibitors such as indinavir and nelfinavir. The compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication.

15 The following references are of interest as background:
Chemical Abstracts No. 33-2525 discloses the preparation of 5-chloro-8-hydroxy-1,6-naphthyridine-7-carboxylic acid amide from the corresponding methyl ester.

20 Derwent Abstract No. 97-048296 is an abstract of Japanese Published Application No. 08301849. The abstract discloses certain heterocyclic carboxamide derivatives. The derivatives are said to be useful as tachykinin receptor inhibitors. *N*-(3,5-bis(trifluoromethyl)benzyl-1,2-dihydro-*N*,2-dimethyl-1-oxo-4-pyrrolidino-3-isoquinoline carboxamide is specifically disclosed.

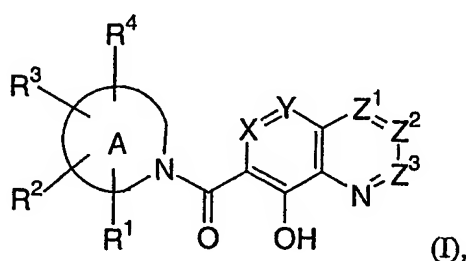
25 WO 98/13350 discloses certain quinoline derivatives which inhibit vascular endothelial growth factor. The reference also discloses certain 1,8-naphthyridine derivatives; i.e., Examples 53 and 54 respectively describe preparations of 2-acetamido-5-(2-fluoro-5-hydroxy-4-methylanilino)-1,8-naphthyridine and 2-amino-5-(2-fluoro-5-hydroxy-4-methylanilino)-1,8-naphthyridine.

WO 99/32450 discloses 4-hydroxyquinoline-2-carboxamide derivatives which are proposed for use in treating herpes virus infections.

30 WO 98/11073 discloses 8-hydroxyquinoline-7carboxamides which are proposed for use in treating herpes virus infections.

SUMMARY OF THE INVENTION

The present invention is directed to novel aza- and polyaza-naphthalenyl carboxamides, in which the carboxamido nitrogen is part of a heterocyclic ring system. These compounds are useful in the inhibition of HIV
 5 integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts or hydrates (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines.
 10 More particularly, the present invention includes a compound of Formula (I):



wherein A is a 5- or 6-membered saturated or unsaturated heterocyclic ring which contains from 1 to 4 nitrogen atoms one of which is directly attached to the exocyclic carbonyl moiety, zero to 2 heteroatoms selected from oxygen and sulfur, and a
 15 balance of carbon atoms; wherein the heterocyclic ring is optionally fused to a phenyl ring or to a second 5- or 6-membered heterocyclic ring which is saturated or unsaturated and which contains from 1 to 4 nitrogen atoms, zero to 2 heteroatoms selected from oxygen and sulfur, and a balance of carbon atoms, wherein the second heterocyclic ring is optionally fused to a phenyl ring;
 20

A is substituted by R¹, R², R³, and R⁴;

X is N or C-Q¹;

25 Y is N or C-Q², provided that X and Y are not both N;

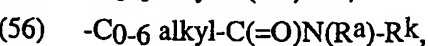
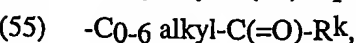
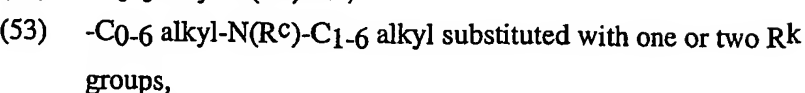
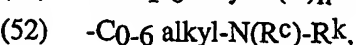
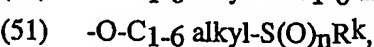
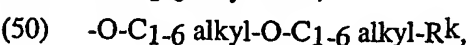
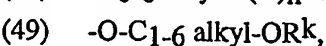
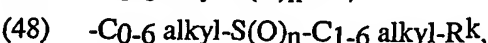
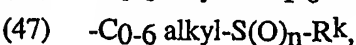
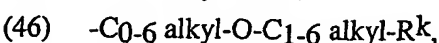
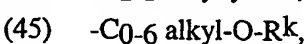
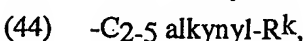
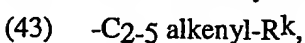
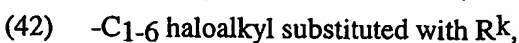
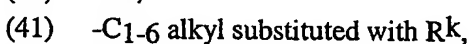
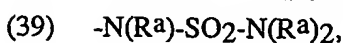
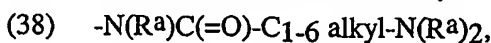
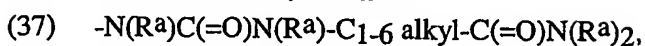
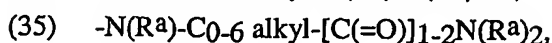
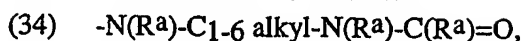
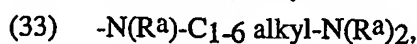
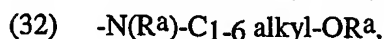
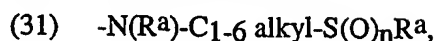
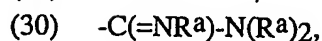
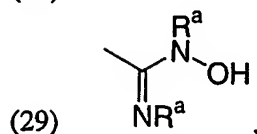
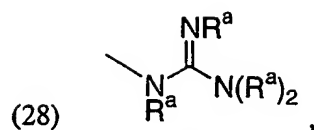
Z¹ is N or C-Q³;

Z² is N or C-Q⁴;

Z³ is N or CH;

5 each of Q¹, Q², Q³, and Q⁴ is independently

- (1) -H,
- (2) -C₁₋₆ alkyl,
- (3) -C₁₋₆ haloalkyl,
- (4) -O-C₁₋₆ alkyl,
- 10 (5) -O-C₁₋₆ haloalkyl,
- (6) halo,
- (7) -CN,
- (8) -C₁₋₆ alkyl-OR^a,
- (9) -C₀₋₆ alkyl-C(=O)R^a,
- 15 (10) -C₀₋₆ alkyl-CO₂R^a,
- (11) -C₀₋₆ alkyl-SR^a,
- (12) -N(R^a)₂,
- (13) -C₁₋₆ alkyl-N(R^a)₂,
- (14) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
- 20 (15) -C₀₋₆ alkyl-G-C₁₋₆ alkyl-C(=O)N(R^a)₂, wherein G is O, S,
N(R^a), or N(SO₂R^a),
- (16) -N(R^a)-C(R^a)=O,
- (17) -C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
- (18) -C(=O)-N(R^a)-C₁₋₆ alkyl-[C(=O)]₀₋₁-N(R^a)₂,
- 25 (19) -C(=O)-N(R^a)-C₁₋₆ alkyl substituted with 1 or 2 -OR^a,
- (20) -C₀₋₆ alkyl-SO₂R^a,
- (21) -C₀₋₆ alkyl-N(R^a)SO₂R^a,
- (22) -C₂₋₆ alkenyl,
- (23) -C₂₋₆ alkenyl-C(=O)-N(R^a)₂,
- 30 (24) -C₂₋₅ alkynyl,
- (25) -C₂₋₅ alkynyl-CH₂N(R^a)₂,
- (26) -C₂₋₅ alkynyl-CH₂OR^a,
- (27) -C₂₋₅ alkynyl-CH₂S(O)_n-R^a, or



- (57) -C₀₋₆ alkyl-N(R^a)C(=O)-R^k,
 (58) -C₀₋₆ alkyl-C(=O)N(R^a)-C₁₋₆ alkyl-R^k, or
 (59) -C₀₋₆ alkyl-N(R^a)-C₀₋₆ alkyl-S(O)_nR^k;

5 each of R¹ and R² is independently:

- (1) -H,
 (2) -C₁₋₆ alkyl,
 (3) -C₁₋₆ haloalkyl,
 (4) -O-C₁₋₆ alkyl,
 10 (5) -O-C₁₋₆ haloalkyl,
 (6) -OH
 (7) halo,
 (8) -NO₂,
 (9) -CN,
 15 (10) -C₁₋₆ alkyl-OR^a,
 (11) -C₀₋₆ alkyl-C(=O)R^a,
 (12) -C₀₋₆ alkyl-CO₂R^a,
 (13) -C₀₋₆ alkyl-SR^a,
 (14) -N(R^a)₂,
 20 (15) -C₁₋₆ alkyl-N(R^a)₂,
 (16) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (17) -C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (18) -SO₂R^a,
 (19) -N(R^a)SO₂R^a,
 25 (20) -C₂₋₅ alkenyl,
 (21) -O-C₁₋₆ alkyl-OR^a,
 (22) -O-C₁₋₆ alkyl-SR^a,
 (23) -O-C₁₋₆ alkyl-NH-CO₂R^a,
 (24) -O-C₂₋₆ alkyl-N(R^a)₂,
 30 (25) -N(R^a)-C₁₋₆ alkyl-SR^a,
 (26) -N(R^a)-C₁₋₆ alkyl-OR^a,
 (27) -N(R^a)-C₁₋₆ alkyl-N(R^a)₂,
 (28) -N(R^a)-C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (29) -R^k,

- (30) -C₁₋₆ alkyl substituted with 1 or 2 R^k groups,
 (31) -C₁₋₆ haloalkyl substituted with 1 or 2 R^k groups,
 (32) -C₂₋₅ alkenyl-R^k,
 (33) -C₂₋₅ alkynyl-R^k,
 5 (34) -O-R^k,
 (35) -O-C₁₋₆ alkyl-R^k,
 (36) -S(O)_n-R^k,
 (37) -S(O)_n-C₁₋₆ alkyl-R^k,
 (38) -O-C₁₋₆ alkyl-OR^k,
 10 (39) -O-C₁₋₆ alkyl-O-C₁₋₆ alkyl-R^k,
 (40) -O-C₁₋₆ alkyl-S(O)_nR^k,
 (41) -C₁₋₆ alkyl (OR^b)(R^k) ,
 (42) -C₁₋₆ alkyl (OR^b)(-C₁₋₆ alkyl-R^k) ,
 (43) -C₀₋₆ alkyl-N(R^b)(R^k),
 15 (44) -C₀₋₆ alkyl-N(R^b)(-C₁₋₆ alkyl-R^k),
 (45) -C₁₋₆ alkyl S(O)_n-R^k,
 (46) -C₁₋₆ alkyl S(O)_n-C₁₋₆ alkyl-R^k,
 (47) -C₀₋₆ alkyl C(O)-R^k, or
 (48) -C₀₋₆ alkyl C(O)-C₁₋₆ alkyl-R^k,
 20

each of R³ and R⁴ is independently

- (1) -H,
 (2) halo,
 (3) -CN,
 25 (4) -NO₂,
 (5) -OH,
 (6) C₁₋₆ alkyl,
 (7) C₁₋₆ haloalkyl,
 (8) -O-C₁₋₆ alkyl,
 30 (9) -O-C₁₋₆ haloalkyl,
 (10) -C₁₋₆ alkyl-OR^a,
 (11) -C₀₋₆ alkyl-C(=O)R^a,
 (12) -C₀₋₆ alkyl-CO₂R^a,
 (13) -C₀₋₆ alkyl-SR^a,

- 5
- (14) $-N(R^a)_2$,
 - (15) $-C_{1-6}$ alkyl- $N(R^a)_2$,
 - (16) $-C_{0-6}$ alkyl- $C(=O)N(R^a)_2$,
 - (17) $-SO_2R^a$,
 - (18) $-N(R^a)SO_2R^a$,
 - (19) $-C_{2-5}$ alkenyl,
 - (20) $-O-C_{1-6}$ alkyl- OR^a ,
 - (21) $-O-C_{1-6}$ alkyl- SR^a ,
 - (22) $-O-C_{1-6}$ alkyl- $NH-CO_2R^a$,

10

 - (23) $-O-C_{2-6}$ alkyl- $N(R^a)_2$, or
 - (24) oxo;

each R^a is independently -H, $-C_{1-6}$ alkyl, or $-C_{1-6}$ haloalkyl;

15 each R^b is independently:

- (1) -H,
- (2) $-C_{1-4}$ alkyl,
- (3) $-C_{1-4}$ haloalkyl,
- (4) $-R^k$,

20

- (5) $-C_{2-3}$ alkenyl,
- (6) $-C_{1-4}$ alkyl- R^k ,
- (7) $-C_{2-3}$ alkenyl- R^k ,
- (8) $-S(O)_n-R^k$, or
- (9) $-C(O)-R^k$;

25

each R^c is independently

- (1) -H,
- (2) $-C_{1-6}$ alkyl,
- (3) $-C_{1-6}$ alkyl substituted with $-N(R^a)_2$, or

30

- (4) $-C_{1-4}$ alkyl-aryl, wherein aryl is optionally substituted with 1 to 5 substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-S-C_{1-6}$ alkyl, -CN, and -OH;

each R^k is independently carbocycle or heterocycle, wherein the carbocycle and heterocycle are unsubstituted or substituted with from 1 to 5 substituents each of which is independently selected from

- | | |
|----|--|
| 5 | (a) halogen,
(b) -C ₁₋₆ alkyl,
(c) -C ₁₋₆ haloalkyl,
(d) -O-C ₁₋₆ alkyl,
(e) -O-C ₁₋₆ haloalkyl,
(f) -S-C ₁₋₆ alkyl, |
| 10 | (g) -CN,
(h) -OH,
(i) oxo,
(j) -C ₀₋₆ alkyl-C(=O)N(R ^a) ₂ ,
(k) -C ₀₋₆ alkyl-C(=O)R ^a , |
| 15 | (l) -N(R ^a)-C(=O)R ^a ,
(m) -N(R ^a)-CO ₂ R ^a ,
(n) -C ₁₋₆ alkyl-N(R ^a)-C(=O)R ^a ,
(o) -N(R ^a) ₂ ,
(p) -C ₁₋₆ alkyl-N(R ^a) ₂ , |
| 20 | (q) -C ₁₋₆ alkyl-OR ^a ,
(r) -C ₀₋₆ alkyl-CO ₂ R ^a ,
(s) -C ₀₋₆ alkyl-O-C ₁₋₆ alkyl-OR ^a ,
(t) -SO ₂ R ^a ,
(u) -SO ₂ N(R ^a) ₂ , |
| 25 | (v) -C ₀₋₆ alkyl-CO ₂ -C ₂₋₅ alkenyl,
(w) aryl,
(x) aryloxy-,
(y) -C ₁₋₄ alkyl substituted with aryl, |
| 30 | (z) heteromonocycle,
(aa) -C ₁₋₄ alkyl substituted with a heteromonocycle,
(bb) heteromonocyclylcarbonyl-C ₀₋₆ alkyl-, and
(cc) N-heteromonocyclyl-N-C ₁₋₆ alkyl-amino-; |
- wherein the aryl group in (w) aryl, (x) aryloxy, and (y) -C₁₋₄ alkyl substituted with aryl, is optionally substituted with from 1 to 4

substituents independently selected from halogen, C₁₋₆ alkyl, -O-C₁₋₆ alkyl, C₁₋₆ alkyl substituted with N(R^a)₂, C₁₋₆ haloalkyl, and -OH; and

5 wherein the heteromonocyclyl group in (z) heteromonocycle, (aa) -C₁₋₄ alkyl substituted with a heteromonocycle, (bb) heteromonocyclyl-carbonyl-C₀₋₆ alkyl-, and (cc) N-heteromonocyclyl-N-C₁₋₆ alkyl-amino- is optionally substituted with from 1 to 4 substituents independently selected from halogen, C₁₋₆ alkyl, -O-C₁₋₆ alkyl, C₁₋₆ haloalkyl, oxo, and -OH; and

10 each n is independently an integer equal to 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

15 The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of preventing AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV.

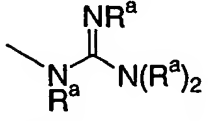
20 Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

25 The present invention includes the aza- and polyaza-naphthalenyl carboxamides of Formula (I) above. These compounds and pharmaceutically acceptable salts thereof are HIV integrase inhibitors.

A first embodiment of the invention is a compound of Formula (I), wherein
30 each of Q¹, Q², Q³ and Q⁴ is independently

- (1) -H,
- (2) -C₁₋₆ alkyl,
- (3) -C₁₋₆ fluoroalkyl,
- (4) -O-C₁₋₆ alkyl,

- (5) -O-C₁₋₆ fluoroalkyl,
 (6) halo,
 (7) -CN,
 (8) -C₁₋₆ alkyl-OR^a,
 5 (9) -C₀₋₆ alkyl-C(=O)R^a,
 (10) -C₀₋₆ alkyl-CO₂R^a,
 (11) -C₀₋₆ alkyl-SR^a,
 (12) -N(R^a)₂,
 (13) -C₁₋₆ alkyl -N(R^a)₂,
 10 (14) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (15) -C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (16) -SO₂R^a,
 (17) -N(R^a)SO₂R^a,
 (18) -C₂₋₅ alkynyl,
 15 (19) -C₂₋₅ alkynyl-CH₂N(R^a)₂,
 (20) -C₂₋₅ alkynyl-CH₂OR^a,
 (21) 
 (22) -N(R^a)-C₁₋₆ alkyl-SR^a,
 (23) -N(R^a)-C₁₋₆ alkyl-OR^a,
 20 (24) -N(R^a)-C₁₋₆ alkyl-N(R^a)₂,
 (25) -N(R^a)-C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (26) -R^k,
 (27) -C₁₋₆ alkyl substituted with R^k,
 (28) -C₁₋₆ fluoroalkyl substituted with R^k,
 25 (29) -C₂₋₅ alkenyl-R^k,
 (30) -C₂₋₅ alkynyl-R^k,
 (31) -O-R^k,
 (32) -O-C₁₋₄ alkyl-R^k,
 (33) -S(O)_n-R^k,
 30 (34) -S(O)_n-C₁₋₄ alkyl-R^k,
 (35) -O-C₁₋₆ alkyl-OR^k,
 (36) -O-C₁₋₆ alkyl-O-C₁₋₄ alkyl-R^k,

- 5
- (37) -O-C₁₋₆ alkyl-SR^k,
 - (38) -N(R^c)-R^k,
 - (39) -N(R^c)-C₁₋₆ alkyl substituted with one or two R^k groups,
 - (40) -N(R^c)-C₁₋₆ alkyl-OR^k,
 - (41) -C(=O)N-C₁₋₆ alkyl-R^k,
 - (42) -C₂₋₅ alkynyl-CH₂S(O)_n-R^a, or
 - (43) -C(=NR^a)-N(R^a)₂;

each of R¹ and R² is independently:

- 10
- (1) -H,
 - (2) -C₁₋₆ alkyl,
 - (3) -C₁₋₆ fluoroalkyl,
 - (4) -O-C₁₋₆ alkyl,
 - (5) -O-C₁₋₆ fluoroalkyl,
- 15
- (6) -OH,
 - (7) halo,
 - (8) -NO₂,
 - (9) -CN,
 - (10) -C₁₋₆ alkyl-OR^a,
- 20
- (11) -C₀₋₆ alkyl-C(=O)R^a,
 - (12) -C₀₋₆ alkylCO₂R^a,
 - (13) -C₀₋₆ alkyl-SR^a,
 - (14) -N(R^a)₂,
 - (15) -C₁₋₆ alkyl N(R^a)₂,
- 25
- (16) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 - (17) -C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 - (18) -SO₂R^a,
 - (19) -N(R^a)SO₂R^a,
 - (20) -C₂₋₅ alkenyl,
- 30
- (21) -O-C₁₋₆ alkyl-OR^a,
 - (22) -O-C₁₋₆ alkyl-SR^a,
 - (23) -O-C₁₋₆ alkyl-NH-CO₂R^a,
 - (24) -O-C₂₋₆ alkyl-N(R^a)₂,
 - (25) -N(R^a)-C₁₋₆ alkyl-SR^a,

- (26) $-N(R^a)-C_{1-6}$ alkyl-OR^a,
 (27) $-N(R^a)-C_{1-6}$ alkyl-N(R^a)₂,
 (28) $-N(R^a)-C_{1-6}$ alkyl-N(R^a)-C(R^a)=O,
 (29) -R^k,
 5 (30) $-C_{1-6}$ alkyl substituted with 1 or 2 R^k groups,
 (31) $-C_{1-6}$ fluoroalkyl substituted with 1 or 2 R^k groups,
 (32) $-C_{2-5}$ alkenyl-R^k,
 (33) $-C_{2-5}$ alkynyl-R^k,
 (34) -O-R^k,
 10 (35) $-O-C_{1-4}$ alkyl-R^k,
 (36) $-S(O)_n-R^k$,
 (37) $-S(O)_n-C_{1-4}$ alkyl-R^k,
 (38) $-O-C_{1-6}$ alkyl-OR^k,
 (39) $-O-C_{1-6}$ alkyl-O-C₁₋₄ alkyl-R^k,
 15 (40) $-O-C_{1-6}$ alkyl-SR^k,
 (41) $-C_{1-6}$ alkyl (OR^b)(R^k) ,
 (42) $-C_{1-6}$ alkyl (OR^b)(-C₁₋₄ alkyl-R^k) ,
 (43) $-C_{0-6}$ alkyl-N(R^b)(R^k),
 (44) $-C_{0-6}$ alkyl-N(R^b)(-C₁₋₄ alkyl-R^k),
 20 (45) $-C_{1-6}$ alkyl S(O)_n-R^k,
 (46) $-C_{1-6}$ alkyl S(O)_n-C₁₋₄ alkyl-R^k,
 (47) $-C_{0-6}$ alkyl C(O)-R^k, or
 (48) $-C_{0-6}$ alkyl C(O)-C₁₋₄ alkyl-R^k,

25 each of R³ and R⁴ is independently

- (1) -H,
 (2) halo,
 (3) -CN,
 (4) -NO₂,
 30 (5) -OH,
 (6) C₁₋₆ alkyl,
 (7) C₁₋₆ fluoroalkyl,
 (8) $-O-C_{1-6}$ alkyl,
 (9) $-O-C_{1-6}$ fluoroalkyl,

- 5
- (10) -C₁₋₆ alkyl-OR^a,
 (11) -C₀₋₆ alkyl-C(=O)R^a,
 (12) -C₀₋₆ alkyl-CO₂R^a,
 (13) -C₀₋₆ alkyl-SR^a,
 (14) -N(R^a)₂,
 (15) -C₁₋₆ alkyl N(R^a)₂,
 (16) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (17) -SO₂R^a,
 (18) -N(R^a)SO₂R^a,
 10 (19) -C₂₋₅ alkenyl,
 (20) -O-C₁₋₆ alkyl-OR^a,
 (21) -O-C₁₋₆ alkyl-SR^a,
 (22) -O-C₁₋₆ alkyl-NH-CO₂R^a,
 (23) -O-C₂₋₆ alkyl-N(R^a)₂, or
 15 (24) oxo

each R^a is independently -H, -C₁₋₆ alkyl, or -C₁₋₆ fluoroalkyl;

each R^b is independently:

- 20 (1) -H,
 (2) -C₁₋₄ alkyl,
 (3) -C₁₋₄ fluoroalkyl,
 (4) -R^k,
 (5) -C₂₋₃ alkenyl,
 25 (6) -C₁₋₄ alkyl-R^k,
 (7) -C₂₋₃ alkenyl-R^k,
 (8) -S(O)_n-R^k, or
 (9) -C(O)-R^k;

30 each R^c is independently

- (1) -H,
 (2) -C₁₋₆ alkyl,
 (3) -C₁₋₆ alkyl substituted with -N(R^a)₂, or

- (4) -C₁₋₄ alkyl-aryl, wherein aryl is optionally substituted with 1 to 5 substituents independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, -O-C₁₋₆ alkyl, -O-C₁₋₆ fluoroalkyl, -S-C₁₋₆ alkyl, -CN, and -OH;

5

each R^k is independently carbocycle or heterocycle, wherein the carbocycle and heterocycle are unsubstituted or substituted with from 1 to 5 substituents each of which is independently selected from

- 10 (a) halogen,
 (b) C₁₋₆ alkyl,
 (c) C₁₋₆ fluoroalkyl,
 (d) -O-C₁₋₆ alkyl,
 (e) -O-C₁₋₆ fluoroalkyl,
 (f) -S-C₁₋₆ alkyl,
 15 (g) -CN,
 (h) -OH,
 (i) oxo,
 (j) -(CH₂)₀₋₃C(=O)N(R^a)₂,
 (k) -(CH₂)₀₋₃C(=O)R^a,
 20 (l) -N(R^a)-C(=O)R^a,
 (m) -N(R^a)-C(=O)OR^a,
 (n) -(CH₂)₁₋₃N(R^a)-C(=O)R^a,
 (o) -N(R^a)₂,
 (p) -C₁₋₆ alkyl-N(R^a)₂,
 25 (q) aryl,
 (r) aryloxy-,
 (s) -C₁₋₄ alkyl substituted with aryl,
 (t) heteromonocycle,
 (u) -C₁₋₄ alkyl substituted with a heteromonocycle,
 30 (v) heteromonocyclylcarbonyl-C₀₋₆ alkyl-, and
 (w) N-heteromonocyclyl-N-C₁₋₆ alkyl-amino-;
 wherein the aryl group in (q) aryl, (r) aryloxy, and (s) -C₁₋₄ alkyl substituted with aryl, is optionally substituted with from 1 to 3 substituents independently selected from halogen, C₁₋₆ alkyl, -O-C₁₋₆

alkyl, C₁₋₆ alkyl substituted with N(R^a)₂, C₁₋₆ fluoroalkyl, and -OH;
and

5 wherein the heteromonocyclyl group in (t) heteromonocycle,
 (u) -C₁₋₄ alkyl substituted with a heteromonocycle,
 (v) heteromonocyclyl-carbonyl-C₀₋₆ alkyl-, and (w) N-
heteromonocyclyl-N-C₁₋₆ alkyl-amino- is optionally substituted with
from 1 to 3 substituents independently selected from halogen, C₁₋₆
alkyl, -O-C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, oxo, and -OH;

10 and all other variables are as originally defined;

or a pharmaceutically acceptable salt thereof.

15 A second embodiment of the invention is a compound of Formula (I),
 wherein

each R^a is independently -H or -C₁₋₆ alkyl;

each R^c is independently

- 20 (1) -H,
 (2) -C₁₋₄ alkyl,
 (3) -C₁₋₄ alkyl substituted with -N(R^a)₂, or
 (4) -C₁₋₄ alkyl-phenyl, wherein the phenyl is optionally substituted
with 1 to 5 substituents independently selected from halogen,
25 C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, -O-C₁₋₆ alkyl, -O-C₁₋₆
fluoroalkyl, -S-C₁₋₆ alkyl, -CN, and -OH;

each R^k is independently:

- 30 (1) aryl selected from phenyl and naphthyl, wherein aryl is
unsubstituted or substituted with from 1 to 5 substituents independently selected from:
 (a) halogen,
 (b) C₁₋₆ alkyl,
 (c) C₁₋₆ fluoroalkyl,
 (d) -O-C₁₋₆ alkyl,

- 5 (e) -O-C₁₋₆ fluoroalkyl,
 (f) phenyl,
 (g) -S-C₁₋₆ alkyl,
 (h) -CN,
 (i) -OH,
 (j) phenyloxy, unsubstituted or substituted with from 1 to 3
 substituents independently selected from:
 (i) halogen,
 (ii) C₁₋₆ alkyl,
 10 (iii) C₁₋₆ fluoroalkyl, and
 (iv) -OH,
 (k) -N(R^a)₂,
 (l) -C₁₋₆ alkyl-N(R^a)₂,
 (m) -R^t,
 15 (p) -(CH₂)₀₋₃C(=O)N(R^a)₂, and
 (q) -(CH₂)₀₋₃C(=O)R^a;
- (2) -C₃₋₇ cycloalkyl, unsubstituted or substituted with from 1 to 3
 substituents independently selected from:
 (a) halogen,
 20 (b) C₁₋₆ alkyl,
 (c) -O-C₁₋₆ alkyl,
 (d) C₁₋₆ fluoroalkyl,
 (e) -O-C₁₋₆ fluoroalkyl,
 (f) -CN,
 25 (h) phenyl, and
 (j) -OH;
- (3) -C₃₋₇ cycloalkyl fused with a phenyl ring, unsubstituted or
 substituted with from 1 to 5 substituents independently selected from:
 (a) halogen,
 30 (b) C₁₋₆ alkyl,
 (c) -O-C₁₋₆ alkyl,
 (d) C₁₋₆ fluoroalkyl,
 (e) -O-C₁₋₆ fluoroalkyl,
 (f) -CN, and

- (g) -OH;
- (4) a 5- or 6- membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heteroaromatic ring is unsubstituted or substituted on nitrogen or carbon with from 1 to 5 substituents independently selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ fluoroalkyl,
 - (d) -O-C₁₋₆ alkyl,
 - (e) -O-C₁₋₆ fluoroalkyl,
 - (f) phenyl,
 - (g) -S-C₁₋₆ alkyl,
 - (h) -CN,
 - (i) -OH,
 - (j) phenoxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
 - (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) C₁₋₆ fluoroalkyl, and
 - (iv) -OH,
 - (k) -N(R^a)₂,
 - (l) -C₁₋₆ alkyl-N(R^a)₂,
 - (m) -R^t,
 - (n) oxo,
 - (o) -(CH₂)₀₋₃C(=O)N(R^a)₂, and
 - (p) -(CH₂)₀₋₃C(=O)R^a;
- (5) a 5- or 6- membered saturated heterocyclic ring containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heterocyclic ring is unsubstituted or substituted with from 1 to 4 substituents independently selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) -O-C₁₋₆ alkyl,
 - (d) C₁₋₆ fluoroalkyl,

- 5 (e) -O-C₁₋₆ fluoroalkyl,
 (f) -CN,
 (g) oxo,
 (h) phenyl
 (i) benzyl,
 (j) phenylethyl,
 (k) -OH,
 (l) -(CH₂)₀₋₃C(=O)N(R^a)₂,
 (m) -(CH₂)₀₋₃C(=O)R^a,
 10 (n) -N(R^a)-C(=O)R^a,
 (o) -N(R^a)-C(=O)OR^a,
 (p) -(CH₂)₁₋₃N(R^a)-C(=O)R^a,
 (q) -N(R^a)₂,
 (r) -(CH₂)₁₋₃N(R^a)₂,
 15 (s) -(CH₂)₀₋₃C(=O)R^t,
 (t) -R^t,
 (u) -N(R^a)R^t, and
 (v) -(CH₂)₁₋₃R^t; or
- (6) an 8- to 10- membered heterobicyclic ring containing from 1 to
 20 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the
 heterobicyclic ring is saturated or unsaturated and is unsubstituted or substituted with
 from 1 to 5 substituents independently selected from:
- 25 (a) halogen,
 (b) C₁₋₆ alkyl,
 (c) -O-C₁₋₆ alkyl,
 (d) C₁₋₆ fluoroalkyl,
 (e) -O-C₁₋₆ fluoroalkyl,
 (f) -CN,
 (g) =O, and
 30 (h) -OH; and

R^t is naphthyl or a 5- or 6-membered heteromonocyclic ring containing from 1 to 4 nitrogen atoms, wherein the heteromonocyclic ring is saturated or unsaturated, and wherein the naphthyl or the heteromonocyclic ring is unsubstituted or substituted with

1 or 2 substituents independently selected from halogen, oxo, C₁₋₄ alkyl, and -O-C₁₋₄ alkyl;

and all other variables are as originally defined;

5

or a pharmaceutically acceptable salt thereof.

A third embodiment is identical to the second embodiment, except that all other variables are as defined in the first embodiment, instead of being as originally defined.

10

A fourth embodiment of the present invention is a compound of Formula I, wherein A is a 5- or 6-membered saturated heterocyclic ring which contains 1 or 2 nitrogen atoms one of which is directly attached to the exocyclic carbonyl moiety, zero or 1 heteroatoms selected from oxygen and sulfur, and a balance of carbon atoms; wherein the heterocyclic ring is optionally fused to a phenyl ring or to a second 5- or 6-membered heterocyclic ring which is saturated or unsaturated and which contains 1 or 2 nitrogen atoms, zero or 1 heteroatoms selected from oxygen and sulfur, and a balance of carbon atoms, wherein the second heterocyclic ring is optionally fused to a phenyl ring;

15

20

and all other variables are as originally defined;

or a pharmaceutically acceptable salt thereof.

25

A fifth embodiment is identical to the fourth embodiment, except that all other variables are as defined in the first embodiment, instead of being as originally defined.

30

A first class of the present invention is compounds of Formula I, wherein A is pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, indolinyl, or isoindolinyl;

and all other variables are as defined in the fourth embodiment;

or a pharmaceutically acceptable salt thereof.

5 A second class is identical to the first class, except that all other variables are as defined in the fifth embodiment, instead of being as defined in the fourth embodiment.

A sixth embodiment of the present invention is a compound of Formula I, wherein

10

X is N;

Y is C-Q²;

15 Z¹ is C-Q³;

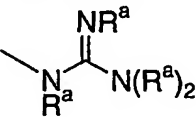
Z² is C-Q⁴;

Z³ is CH;

20

Q² is

- | | | |
|----|------|--|
| | (1) | -H, |
| | (2) | -C ₁₋₆ alkyl, |
| | (3) | -C ₁₋₆ fluoroalkyl, |
| 25 | (4) | -O-C ₁₋₆ alkyl, |
| | (5) | -O-C ₁₋₆ fluoroalkyl, |
| | (6) | halo, |
| | (7) | -CN, |
| | (8) | -C ₁₋₆ alkyl-OR ^a , |
| 30 | (9) | -C ₀₋₆ alkyl-C(=O)R ^a , |
| | (10) | -C ₀₋₆ alkyl-CO ₂ R ^a , |
| | (11) | -C ₀₋₆ alkyl-SR ^a , |
| | (12) | -N(R ^a) ₂ , |
| | (13) | -C ₁₋₆ alkyl -N(R ^a) ₂ , |

- (14) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (15) -C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (16) -SO₂R^a,
 (17) -N(R^a)SO₂R^a,
 5 (18) -C₂₋₅ alkynyl,
 (19) -C₂₋₅ alkynyl-CH₂N(R^a)₂,
 (20) -C₂₋₅ alkynyl-CH₂OR^a,
 (21) ,
 (22) -N(R^a)-C₁₋₆ alkyl-SR^a,
 10 (23) -N(R^a)-C₁₋₆ alkyl-OR^a,
 (24) -N(R^a)-C₁₋₆ alkyl-N(R^a)₂,
 (25) -N(R^a)-C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (26) -R^k,
 (27) -C₁₋₆ alkyl substituted with R^k,
 15 (28) -C₁₋₆ fluoroalkyl substituted with R^k,
 (29) -C₂₋₅ alkenyl-R^k,
 (30) -C₂₋₅ alkynyl-R^k,
 (31) -O-R^k,
 (32) -O-C₁₋₄ alkyl-R^k,
 20 (33) -S(O)_n-R^k,
 (34) -S(O)_n-C₁₋₄ alkyl-R^k,
 (35) -O-C₁₋₆ alkyl-OR^k,
 (36) -O-C₁₋₆ alkyl-O-C₁₋₄ alkyl-R^k,
 (37) -O-C₁₋₆ alkyl-SR^k,
 25 (38) -N(R^c)-R^k,
 (39) -N(R^c)-C₁₋₆ alkyl substituted with one or two R^k groups,
 (40) -N(R^c)-C₁₋₆ alkyl-OR^k,
 (41) -C(=O)N-C₁₋₆ alkyl-R^k,
 (42) -C₂₋₅ alkynyl-CH₂S(O)_n-R^a, or
 30 (43) -C(=NR^a)-N(R^a)₂;

each of Q³ and Q⁴ is independently:

- 5
- (1) -H,
 - (2) -C₁₋₆ alkyl,
 - (3) -C₁₋₆ fluoroalkyl,
 - (4) -O-C₁₋₆ alkyl,
 - (5) -O-C₁₋₆ fluoroalkyl,
 - (6) halo,
 - (7) -CN,
 - (8) -C₁₋₆ alkyl-OR^a,
 - (9) -C₀₋₆ alkyl-C(=O)R^a,

10

 - (10) -C₀₋₆ alkyl-CO₂R^a,
 - (11) -SR^a,
 - (12) -N(R^a)₂,
 - (13) -C₁₋₆ alkyl -N(R^a)₂,
 - (14) -C₀₋₆ alkyl-C(=O)N(R^a)₂,

15

 - (15) -SO₂R^a,
 - (16) -N(R^a)SO₂R^a
 - (17) -R^k, or
 - (18) -C₁₋₆ alkyl substituted with R^k;

20 and all other variables are as originally defined;

or a pharmaceutically acceptable salt thereof.

25 A seventh embodiment is identical to the sixth embodiment, except that all other variables are as defined in the first embodiment, instead of being as originally defined.

An eighth embodiment of the present invention is a compound of Formula I, wherein

30 Q³ is:

- (1) -H,
- (2) -C₁₋₆ alkyl,
- (3) -C₁₋₆ fluoroalkyl,

- 5
- (4) -O-C₁₋₆ alkyl,
 (5) -O-C₁₋₆ fluoroalkyl,
 (6) halo,
 (7) -CN,
 (8) -C₁₋₆ alkyl-OR^a,
 (9) -C₀₋₆ alkyl-C(=O)R^a,
 (10) -C₀₋₆ alkyl-CO₂R^a,
 (11) -SR^a,
 (12) -N(R^a)₂,
 10 (13) -C₁₋₆ alkyl -N(R^a)₂,
 (14) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (15) -SO₂R^a,
 (16) -N(R^a)SO₂R^a
 (17) -R^k, or
 15 (18) -C₁₋₆ alkyl substituted with R^k;

Q⁴ is:

- 20
- (1) -H,
 (2) -C₁₋₆ alkyl,
 (3) -C₁₋₆ fluoroalkyl,
 (4) -O-C₁₋₆ alkyl,
 (5) -O-C₁₋₆ fluoroalkyl,
 (6) halo,
 (7) -CN,
 25 (8) -C₁₋₆ alkyl-OR^a,
 (9) -C₀₋₆ alkyl-C(=O)R^a,
 (10) -C₀₋₆ alkyl-CO₂R^a,
 (11) -SR^a,
 (12) -N(R^a)₂,
 30 (13) -C₁₋₆ alkyl -N(R^a)₂,
 (14) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (15) -SO₂R^a, or
 (16) -N(R^a)SO₂R^a;

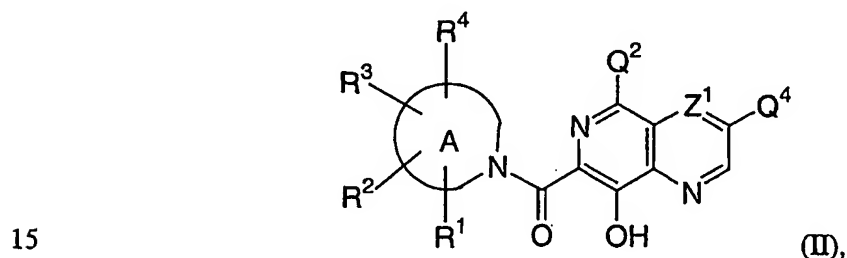
and all other variables are as defined in the sixth embodiment;

or a pharmaceutically acceptable salt thereof.

- 5 A ninth embodiment is identical to the eighth embodiment, except that all other variables are as defined in the seventh embodiment, instead of being as defined in the sixth embodiment.

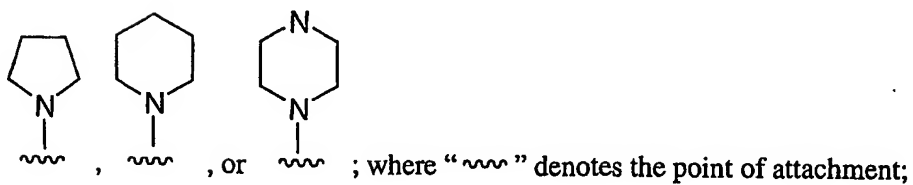
- 10 In an aspect of each of the eighth and ninth embodiments, Q^3 and Q^4 are both -H.

A tenth embodiment of the present invention is a compound of Formula II:



wherein

- 20 A is



Z^1 is N or C- Q^3 ;

Q² is

- (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -C₁₋₄ fluoroalkyl,
- 5 (4) -O-C₁₋₄ alkyl,
- (5) -O-C₁₋₄ fluoroalkyl,
- (6) halo,
- (7) -CN,
- (8) -C₁₋₄ alkyl-OR^a,
- 10 (9) -(CH₂)₀₋₂C(=O)R^a,
- (10) -(CH₂)₀₋₂CO₂R^a,
- (11) -(CH₂)₀₋₂SR^a,
- (12) -N(R^a)₂,
- (13) -C₁₋₄ alkyl -N(R^a)₂,
- 15 (14) -(CH₂)₀₋₂C(=O)N(R^a)₂,
- (15) -SO₂R^a,
- (16) -N(R^a)SO₂R^a,
- (17) -C₂₋₃ alkynyl,
- (18) —C≡C—CH₂N(R^a)₂,
- 20 (19) —C≡C—CH₂OR^a,
- (20) -N(R^a)-C₁₋₄ alkyl-SR^a,
- (21) -N(R^a)-C₁₋₄ alkyl-OR^a,
- (22) -N(R^a)-C₁₋₄ alkyl-N(R^a)₂,
- (23) -N(R^a)-C₁₋₄ alkyl-N(R^a)-C(R^a)=O,
- 25 (24) -R^k,
- (25) -C₁₋₄ alkyl substituted with R^k,
- (26) -C₁₋₄ fluoroalkyl substituted with R^k,
- (27) -C₂₋₅ alkenyl-R^k,
- (28) -C₂₋₅ alkynyl-R^k,
- 30 (29) -O-R^k,
- (30) -O-C₁₋₄ alkyl-R^k,
- (31) -S(O)_n-R^k,
- (32) -N(R^c)-R^k,
- (33) -N(R^c)-C₁₋₄ alkyl substituted with one or two R^k groups,

(34) $-N(R^c)-C_{1-4} \text{ alkyl}-OR^k$,

(35) $-C(=O)N-C_{1-4} \text{ alkyl}-R^k$,

(36) $—C\equiv C-CH_2SR^a$, or

(37) $—C\equiv C-CH_2SO_2R^a$;

5

Q³ is

(1) $-H$,

(2) $-C_{1-4} \text{ alkyl}$,

(3) $-C_{1-4} \text{ fluoroalkyl}$,

10

(4) $-O-C_{1-4} \text{ alkyl}$,

(5) $-O-C_{1-4} \text{ fluoroalkyl}$,

(6) halo selected from $-F$, $-Cl$, and $-Br$,

(7) $-CN$,

(8) $-C_{1-4} \text{ alkyl}-OR^a$, or

15

(9) $-C_{1-4} \text{ alkyl}$ substituted with R^k ;

Q⁴ is:

(1) $-H$,

(2) $-C_{1-4} \text{ alkyl}$,

20

(3) $-C_{1-4} \text{ fluoroalkyl}$,

(4) $-O-C_{1-4} \text{ alkyl}$,

(5) $-O-C_{1-4} \text{ fluoroalkyl}$,

(6) halo selected from $-F$, $-Cl$, and $-Br$,

(7) $-CN$,

25

(8) $-C_{1-6} \text{ alkyl}-OR^a$,

(9) $-N(R^a)_2$, or

(10) $-C_{1-6} \text{ alkyl}-N(R^a)_2$;

each of R^1 and R^2 is independently:

30

(1) $-H$,

(2) $-C_{1-4} \text{ alkyl}$,

(3) $-C_{1-4} \text{ fluoroalkyl}$,

(4) $-O-C_{1-4} \text{ alkyl}$,

(5) $-O-C_{1-4} \text{ fluoroalkyl}$,

- (6) -OH,
 (7) halo,
 (8) -CN,
 (9) -C₁₋₄ alkyl-OR^a,
 5 (10) -(CH₂)₀₋₂C(=O)R^a,
 (11) -(CH₂)₀₋₂CO₂R^a,
 (12) -(CH₂)₀₋₂SR^a,
 (13) -N(R^a)₂,
 (14) -C₁₋₄ alkyl N(R^a)₂,
 10 (15) -(CH₂)₀₋₂C(=O)N(R^a)₂,
 (16) -C₁₋₄ alkyl-N(R^a)-C(R^a)=O,
 (17) -SO₂R^a,
 (18) -N(R^a)SO₂R^a,
 (19) -O-C₁₋₄ alkyl-OR^a,
 15 (20) -O-C₁₋₄ alkyl-SR^a,
 (21) -O-C₁₋₄ alkyl-NH-CO₂R^a,
 (22) -O-C₂₋₄ alkyl-N(R^a)₂,
 (23) -N(R^a)-C₁₋₄ alkyl-SR^a,
 (24) -N(R^a)-C₁₋₄ alkyl-OR^a,
 20 (25) -N(R^a)-C₁₋₄ alkyl-N(R^a)₂,
 (26) -N(R^a)-C₁₋₄ alkyl-N(R^a)-C(R^a)=O,
 (27) -R^k,
 (28) -C₁₋₄ alkyl substituted with 1 or 2 R^k groups,
 (29) -C₁₋₄ fluoroalkyl substituted with 1 or 2 R^k groups,
 25 (30) -O-R^k,
 (31) -O-C₁₋₄ alkyl-R^k,
 (32) -S(O)_n-R^k,
 (33) -S(O)_n-C₁₋₄ alkyl-R^k,
 (34) -O-C₁₋₄ alkyl-OR^k,
 30 (35) -O-C₁₋₄ alkyl-O-C₁₋₄ alkyl-R^k,
 (36) -O-C₁₋₄ alkyl-SR^k, or
 (37) -C₀₋₄ alkyl-N(R^b)(R^k);

each of R³ and R⁴ is independently

- 5
- (1) -H,
 - (2) halo,
 - (3) -CN,
 - (4) -OH,
 - (5) C₁₋₄ alkyl,
 - (6) C₁₋₄ fluoroalkyl,
 - (7) -O-C₁₋₄ alkyl,
 - (8) -O-C₁₋₄ fluoroalkyl,
 - (9) -C₁₋₄ alkyl-OR^a,
 - 10 (10) -O-C₁₋₄ alkyl-OR^a,
 - (11) -O-C₁₋₄ alkyl-SR^a,
 - (12) -O-C₁₋₄ alkyl-NH-CO₂R^a, or
 - (13) -O-C₂₋₄ alkyl-N(R^a)₂;

15 each R^a is independently -H or -C₁₋₄ alkyl;

each R^b is independently:

- 20
- (1) -H,
 - (2) -C₁₋₄ alkyl,
 - (3) -C₁₋₄ fluoroalkyl,
 - (4) -R^k,
 - (5) -C₁₋₄ alkyl-R^k,
 - (6) -S(O)_n-R^k, or
 - (7) -C(=O)-R^k;

25

each R^c is independently

- 30
- (1) -H,
 - (2) -C₁₋₄ alkyl,
 - (3) -C₁₋₄ alkyl substituted with -N(R^a)₂, or
 - (4) -C₁₋₄ alkyl-phenyl, wherein the phenyl is optionally substituted with 1 to 3 substituents independently selected from halogen, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, -O-C₁₋₄ alkyl, -O-C₁₋₄ fluoroalkyl, -S-C₁₋₄ alkyl, -CN, and -OH;

each R^k is independently:

- (1) aryl selected from phenyl and naphthyl, wherein aryl is unsubstituted or substituted with from 1 to 5 substituents independently selected from:
- (a) halogen,
 - (b) C_{1-6} alkyl,
 - (c) C_{1-6} fluoroalkyl,
 - (d) $-O-C_{1-6}$ alkyl,
 - (e) $-O-C_{1-6}$ fluoroalkyl,
 - (f) phenyl,
 - (g) $-S-C_{1-6}$ alkyl,
 - (h) $-CN$,
 - (i) $-OH$,
 - (j) phenoxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
 - (i) halogen,
 - (ii) C_{1-6} alkyl,
 - (iii) C_{1-6} fluoroalkyl, and
 - (iv) $-OH$,
 - (k) $-N(R^a)_2$,
 - (l) $-C_{1-6}$ alkyl- $N(R^a)_2$,
 - (m) $-R^t$,
 - (p) $-(CH_2)_0-3C(=O)N(R^a)_2$, and
 - (q) $-(CH_2)_0-3C(=O)R^a$;
- (2) $-C_{3-7}$ cycloalkyl, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
- (a) halogen,
 - (b) C_{1-6} alkyl,
 - (c) $-O-C_{1-6}$ alkyl,
 - (d) C_{1-6} fluoroalkyl,
 - (e) $-O-C_{1-6}$ fluoroalkyl,
 - (f) $-CN$,
 - (h) phenyl, and
 - (j) $-OH$;

- (3) -C₃₋₇ cycloalkyl fused with a phenyl ring, unsubstituted or substituted with from 1 to 5 substituents independently selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) -O-C₁₋₆ alkyl,
 - (d) C₁₋₆ fluoroalkyl,
 - (e) -O-C₁₋₆ fluoroalkyl,
 - (f) -CN, and
 - (g) -OH;
- (4) a 5- or 6- membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heteroaromatic ring is unsubstituted or substituted on nitrogen or carbon with from 1 to 5 substituents independently selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ fluoroalkyl,
 - (d) -O-C₁₋₆ alkyl,
 - (e) -O-C₁₋₆ fluoroalkyl,
 - (f) phenyl,
 - (g) -S-C₁₋₆ alkyl,
 - (h) -CN,
 - (i) -OH,
 - (j) phenyloxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
 - (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) C₁₋₆ fluoroalkyl, and
 - (iv) -OH,
 - (k) -N(R^a)₂,
 - (l) -C₁₋₆ alkyl-N(R^a)₂,
 - (m) -R^t,
 - (n) oxo,
 - (o) -(CH₂)₀₋₃C(=O)N(R^a)₂, and
 - (p) -(CH₂)₀₋₃C(=O)R^a;

(5) a 5- or 6- membered saturated heterocyclic ring containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heterocyclic ring is unsubstituted or substituted with from 1 to 4 substituents independently selected from:

- 5 (a) halogen,
- (b) C₁₋₆ alkyl,
- (c) -O-C₁₋₆ alkyl,
- (d) C₁₋₆ fluoroalkyl,
- (e) -O-C₁₋₆ fluoroalkyl,
- 10 (f) -CN,
- (g) oxo,
- (h) phenyl,
- (i) benzyl,
- (j) phenylethyl,
- 15 (k) -OH,
- (l) -(CH₂)₀₋₃C(=O)N(R^a)₂,
- (m) -(CH₂)₀₋₃C(=O)R^a,
- (n) -N(R^a)-C(=O)R^a,
- (o) -N(R^a)-C(=O)OR^a,
- 20 (p) -(CH₂)₁₋₃N(R^a)-C(=O)R^a,
- (q) -N(R^a)₂,
- (r) -(CH₂)₁₋₃N(R^a)₂,
- (s) -(CH₂)₀₋₃C(=O)R^t,
- (t) -R^t,
- 25 (u) -N(R^a)R^t, and
- (v) -(CH₂)₁₋₃R^t; or

(6) an 8- to 10- membered heterobicyclic ring containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heterobicyclic ring is saturated or unsaturated, and is unsubstituted or substituted with from 1 to 5 substituents independently selected from:

- (a) halogen,
- (b) C₁₋₆ alkyl,
- (c) -O-C₁₋₆ alkyl,
- (d) C₁₋₆ fluoroalkyl,

- (e) -O-C₁₋₆ fluoroalkyl,
- (f) -CN,
- (g) =O, and
- (h) -OH;

5

R^t is naphthyl or a 5- or 6-membered heteromonocyclic ring containing from 1 to 4 nitrogen atoms, wherein the heteromonocyclic ring is saturated or unsaturated, and wherein the naphthyl or the heteromonocyclic ring is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, oxo, C₁₋₄ alkyl, and -O-C₁₋₄ alkyl; and

10

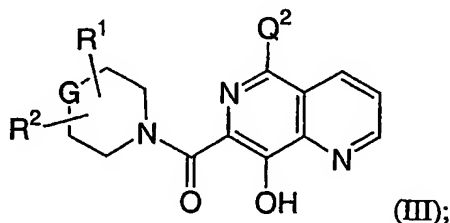
n is an integer equal to 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

15

In an aspect of the tenth embodiment, Z¹ is CH, and Q⁴ is -H.

A third class of the present invention is compounds of Formula III:



20

wherein G is:

- (1) NH optionally substituted by either R¹ or R²,
- (2) CH₂ optionally substituted by either or both R¹ and R², or
- (3) -S(O)_n wherein n is an integer equal to zero, 1 or 2;

25

Q² is

- (1) -H,
- (2) methyl,

- 5 (3) ethyl,
 (4) CF_3 ,
 (5) methoxy,
 (6) ethoxy
 (7) $-\text{OCF}_3$
 (8) halo selected from -F, -Cl and -Br,
 (9) $-\text{CN}$,
 (10) $-\text{CH}_2\text{OH}$,
 (11) $-\text{CH}_2\text{OCH}_3$
 (12) $-(\text{CH}_2)_{0-2}\text{CO}_2\text{CH}_3$,
 (13) $-\text{SR}^a$,
 (14) $-\text{N}(\text{R}^a)_2$,
 (15) $-\text{SO}_2\text{R}^a$,
 (16) $-\text{C}\equiv\text{C}-\text{CH}_2\text{OR}^a$,
 (17) $-\text{N}(\text{R}^a)-(\text{CH}_2)_{1-3}\text{SR}^a$,
 (18) $-\text{N}(\text{R}^a)-(\text{CH}_2)_{1-3}\text{OR}^a$,
 (19) $-\text{N}(\text{R}^a)-(\text{CH}_2)_{1-3}\text{N}(\text{R}^a)_2$,
 (20) $-\text{N}(\text{R}^a)-(\text{CH}_2)_{1-3}\text{N}(\text{R}^a)-\text{C}(\text{R}^a)=\text{O}$,
 (21) $-\text{R}^k$,
 (22) $-(\text{CH}_2)_{1-4}\text{R}^k$,
 (23) $-\text{C}\equiv\text{C}-\text{CH}_2\text{R}^k$,
 (24) $-\text{O}-\text{R}^k$,
 (25) $-\text{S}-\text{R}^k$,
 (26) $-\text{SO}_2-\text{R}^k$,
 (27) $-\text{N}(\text{R}^c)-\text{R}^k$,
 (28) $-\text{N}(\text{R}^c)-(\text{CH}_2)_{1-4}\text{H}$ substituted with one or two R^k groups,
 (29) $-\text{N}(\text{R}^c)-(\text{CH}_2)_{1-4}\text{OR}^k$,
 (30) $-\text{C}(=\text{O})\text{N}-(\text{CH}_2)_{1-4}\text{R}^k$,
 (31) $-\text{C}\equiv\text{C}-\text{CH}_2\text{SR}^a$, or
 30 (32) $-\text{C}\equiv\text{C}-\text{CH}_2\text{SO}_2\text{R}^a$;

each of R^1 and R^2 is independently:

- (1) $-\text{H}$,
 (2) methyl,

- 5
- (3) ethyl,
 - (4) CF_3 ,
 - (5) methoxy,
 - (6) ethoxy
 - (7) $-\text{OCF}_3$
 - (8) halo selected from -F, -Cl and -Br,
 - (9) -CN,
 - (10) $-\text{CH}_2\text{OR}^a$,
 - (11) $-\text{CO}_2\text{R}^a$,
 - 10 (12) $-\text{SR}^a$,
 - (13) $-\text{N}(\text{R}^a)_2$,
 - (14) $-(\text{CH}_2)_{1-3}\text{N}(\text{R}^a)_2$,
 - (15) $-\text{SO}_2\text{R}^a$,
 - (16) $-(\text{CH}_2)_{1-2}\text{N}(\text{R}^a)-\text{C}(\text{R}^a)=\text{O}$,
 - 15 (17) $-\text{R}^k$,
 - (18) $-(\text{CH}_2)_{1-3}\text{H}$ substituted with 1 or 2 R^k groups,
 - (19) $-\text{O}-\text{R}^k$, or
 - (20) $-\text{O}-(\text{CH}_2)_{1-3}\text{R}^k$;

20 each R^a is independently -H or $-\text{C}_{1-4}$ alkyl;

each R^c is independently -H, $-\text{C}_{1-4}$ alkyl, or $-(\text{CH}_2)_{1-3}\text{N}(\text{R}^a)_2$;

each R^k is independently:

- 25 (1) phenyl which is unsubstituted or substituted with from 1 to 4 substituents independently selected from:
- (a) halogen selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) $-\text{CF}_3$,
 - 30 (d) methoxy,
 - (e) $-\text{OCF}_3$,
 - (f) phenyl,
 - (g) $-\text{S}-\text{CH}_3$,
 - (h) -CN,

- (i) -OH,
- (j) phenoxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
- 5 (i) halogen selected from -F, -Cl, and -Br,
- (ii) methyl,
- (iii) -CF₃, and
- (iv) -OH,
- (k) -N(R^a)₂,
- (l) -(CH₂)₁₋₃N(R^a)₂,
- 10 (m) -R^t,
- (p) -(CH₂)₀₋₃C(=O)N(R^a)₂, and
- (q) -(CH₂)₀₋₃C(=O)R^a;
- (2) -C₃₋₆ cycloalkyl, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
- 15 (a) halogen selected from -F, -Cl, and -Br,
- (b) methyl,
- (c) -CF₃,
- (d) methoxy,
- (e) -OCF₃,
- 20 (f) -CN,
- (h) phenyl, and
- (j) -OH;
- (3) a 5- or 6- membered heteroaromatic ring selected from thienyl, pyridyl, imidazolyl, pyrrolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, furanyl, and pyridazinyl, wherein the heteroaromatic ring is unsubstituted or substituted on nitrogen or carbon with 1 or 2 substituents independently selected from:
- 25 (a) halogen selected from -F, -Cl, and -Br,
- (b) methyl,
- 30 (c) -CF₃,
- (d) methoxy,
- (e) -OCF₃,
- (f) phenyl,
- (g) -S-C₁₋₆ alkyl,

- (h) -CN,
 (i) -OH,
 (j) phenyloxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
 5 (i) halogen selected from -F, -Cl, and -Br,
 (ii) methyl,
 (iii) -CF₃, and
 (iv) -OH,
 (k) -N(R^a)₂,
 10 (l) -C₁₋₆ alkyl-N(R^a)₂,
 (m) -R^t,
 (n) oxo,
 (o) -(CH₂)₀₋₃C(=O)N(R^a)₂, and
 (p) -(CH₂)₀₋₃C(=O)R^a;
 15 (4) a 5- or 6- membered saturated heterocyclic ring selected from piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, and pyrazolidinyl, wherein the heterocyclic ring is unsubstituted or substituted with 1 or 2 substituents independently selected from:
 20 (a) halogen selected from -F, -Cl, and -Br,
 (b) methyl,
 (c) -CF₃,
 (d) methoxy,
 (e) -OCF₃,
 25 (f) -CN,
 (g) =O,
 (h) phenyl,
 (i) benzyl,
 (j) phenylethyl,
 30 (k) -OH,
 (l) -(CH₂)₀₋₃C(=O)N(R^a)₂,
 (m) -(CH₂)₀₋₃C(=O)R^a,
 (n) N(R^a)-C(=O)R^a,
 (o) N(R^a)-C(=O)OR^a,

- 5
- (p) $(\text{CH}_2)_{1-3}\text{N}(\text{R}^a)\text{-C(=O)R}^a$,
 - (q) $\text{N}(\text{R}^a)_2$,
 - (r) $(\text{CH}_2)_{1-3}\text{N}(\text{R}^a)_2$,
 - (s) $\text{-(CH}_2\text{)}_{0-3}\text{C(=O)R}^t$,
 - (t) -R^t ,
 - (u) $\text{-N}(\text{R}^a)\text{R}^t$, and
 - (v) $\text{-(CH}_2\text{)}_{1-3}\text{R}^t$; and

(5) an 8- to 10- membered heterobicyclic ring selected from indolyl, benzotriazolyl, benzoimidazolyl, imidazo[4,5-b]pyridinyl, dihydroimidazo[4,5-b]pyridinyl, pyrazolo[4,3-c]pyridinyl, dihydropyrazolo[4,3-c]pyridinyl, tetrahydropyrazolo[4,3-c]pyridinyl, pyrrolo[1,2-a]pyrazinyl, dihydropyrrolo[1,2-a]pyrazinyl, tetrahydropyrrolo[1,2-a]pyrazinyl, octahydropyrrolo[1,2-a]pyrazinyl, isoindolyl, indazolyl, indolyl, isoindolyl, quinolyl, isoquinolyl, quinoxalyl, quinazolyl, cinnolyl, chromanyl, and isochromanyl, wherein the bicyclic ring is unsubstituted or substituted with 1 or 2 substituents independently selected from:

- 20
- (a) halogen selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) -CF_3 ,
 - (d) methoxy,
 - (e) -OCF_3 ,
 - (f) -CN ,
 - (g) =O , and
 - (h) -OH ; and

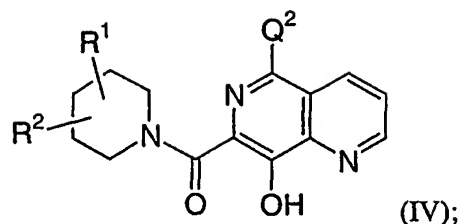
25

R^t is selected from pyrrolidinyl, pyrazolidinyl, imidazolyl, piperidinyl, piperazinyl, pyrrolyl, pyridyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, and pyradizyl; any one of which is unsubstituted or substituted with 1 or 2 substituents independently selected from -F, -Cl, -Br, oxo, methyl, and methoxy;

30

or a pharmaceutically acceptable salt thereof.

A sub-class of the present invention is compounds of Formula (IV):



wherein each of the variables is as defined in the third class of the invention;

5 or a pharmaceutically acceptable salt thereof.

Exemplary compounds of the invention include compounds selected from the group consisting of

10 7-[(3-phenylpyrrolidin-1-yl)carbonyl]-1,6-naphthyridin-8-ol;

7-[(3-benzylpiperidin-1-yl)carbonyl]-1,6-naphthyridin-8-ol;

and pharmaceutically acceptable salts thereof.

15

Other embodiments of the invention include compounds of Formula (I), (II), (III), or (IV), wherein each variable is independently as defined in any one of the preceding embodiments, classes, sub-classes or aspects.

Other embodiments of the present invention include the following:

20

(a) A pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse

25

transcriptase inhibitors.

(c) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of Formula (I).

(d) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of Formula (I).

5 (e) The method of (d), wherein the compound of Formula (I) is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

10 (f) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of a compound of Formula (I).

(g) The method of (f), wherein the compound is administered in combination with a therapeutically effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors

15 (h) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the composition of (a) or (b).

(i) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the composition of (a) or (b).

(j) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the composition of (a) or (b).

25 Still other embodiments of the present invention include the following:

(k) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier.

30 (l) A combination useful for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS, which is a therapeutically effective amount of a compound of Formula (I) and a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(m) The combination of (l), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

5 Additional embodiments of the invention include the pharmaceutical compositions and methods set forth in (a)-(j) above and the compositions and combinations set forth in (k)-(m), wherein the compound employed therein is a compound of one of the embodiments, classes, sub-classes, or aspects of compounds described above. In all of these embodiments, the compound may optionally be used
10 in the form of a pharmaceutically acceptable salt.

As used herein, the term "C₁₋₆ alkyl" (or "C₁-C₆ alkyl") means linear or branched chain alkyl groups having from 1 to 6 carbon atoms and includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. "C₁₋₄ alkyl" means n-, iso-, sec- and t-butyl, n- and
15 isopropyl, ethyl and methyl.

The term "C₀" as employed in expressions such as "C₀₋₆ alkyl" means a direct covalent bond.

The term "C₂₋₅ alkenyl" (or "C₂-C₅ alkenyl") means linear or branched chain alkenyl groups having from 2 to 5 carbon atoms and includes all of
20 the pentenyl isomers as well as 1-butenyl, 2-butenyl, 3-butenyl, isobutenyl, 1-propenyl, 2-propenyl, and ethenyl (or vinyl). Similar terms such as "C₂₋₃ alkenyl" have an analogous meaning.

The term "C₂₋₅ alkynyl" (or "C₂-C₅ alkynyl") means linear or branched chain alkynyl groups having from 2 to 5 carbon atoms and includes all of
25 the pentynyl isomers as well as 1-butyne, 2-butyne, 3-butyne, 1-propyne, 2-propyne, and ethyne (or acetylene). Similar terms such as "C₂₋₃ alkynyl" have an analogous meaning.

The term "C₃₋₇ cycloalkyl" (or "C₃-C₇ cycloalkyl") means a cyclic ring of an alkane having three to seven total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl). The term "C₃₋₆ cycloalkyl"
30 refers to a cyclic ring selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Terms such as "C₃₋₅ cycloalkyl" have an analogous meaning.

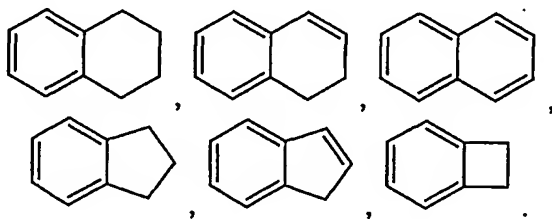
The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively, fluoro, chloro, bromo, and iodo).

The term "thio" (also referred to as "thioxo") means divalent sulfur; i.e., =S.

The term "C₁₋₆ haloalkyl" (which may alternatively be referred to as "C_{1-C6} haloalkyl" or "halogenated C_{1-C6} alkyl") means a C₁ to C₆ linear or
5 branched alkyl group as defined above with one or more halogen substituents. The term "C₁₋₄ haloalkyl" has an analogous meaning.

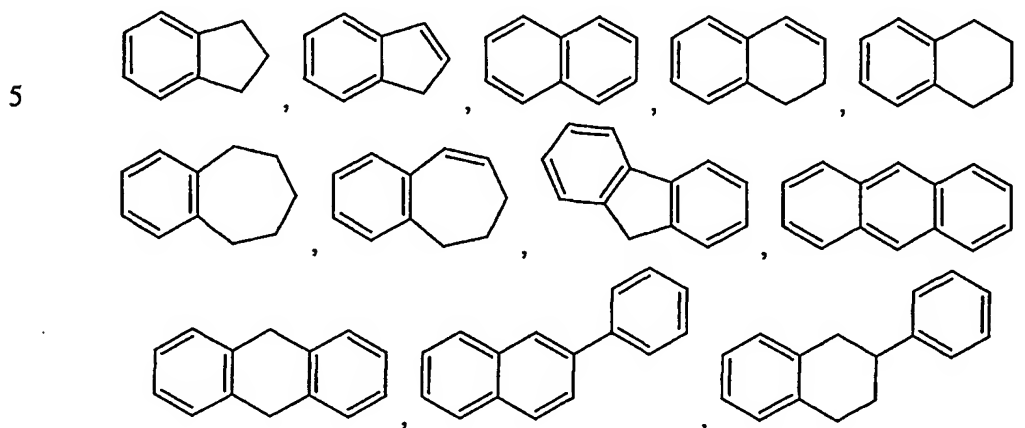
The term "C₁₋₆ fluoroalkyl" (which may alternatively be referred to as "C_{1-C6} fluoroalkyl" or "fluorinated C_{1-C6} alkyl") means a C₁ to C₆ linear or
10 branched alkyl group as defined above with one or more fluorine substituents. The term "C₁₋₄ fluoroalkyl" (or "C_{1-C4} fluoroalkyl" or "fluorinated C_{1-C4} alkyl") has an analogous meaning. Representative examples of suitable fluoroalkyls include the series (CH₂)₀₋₄CF₃ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.), 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 3,3,3-trifluoroisopropyl, 1,1,1,3,3,3-hexafluoroisopropyl, and perfluorohexyl.

15 The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein broadly refers to a C₃ to C₈ monocyclic, saturated or unsaturated ring or a C₇ to C₁₂ bicyclic ring system in which the rings are independent or fused and in which each ring is saturated or unsaturated. The carbocycle may be attached at any carbon atom which results in a stable compound.
20 The fused bicyclic carbocycles are a subset of the carbocycles; i.e., the term "fused bicyclic carbocycle" generally refers to a C₇ to C₁₀ bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms are shared by each of the rings in the ring system. A subset of the fused bicyclic carbocycles are the fused bicyclic carbocycles in which one ring is a benzene ring and the other ring is
25 saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include the following:



30

As used herein, the term "fused carbocyclic ring system" refers to a carbocycle as defined above which is fused to a phenyl ring. Representative examples include:



10 The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the polyring systems may be fused or attached to each other via a single bond. Suitable aryl groups include, but are not limited to, phenyl, naphthyl, and biphenylenyl.

15 The term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") broadly refers to a 4- to 8-membered monocyclic ring, 7- to 12-membered bicyclic ring system, or an 11 to 16-membered tricyclic ring system, any ring of which is saturated or unsaturated, and which consists of carbon atoms and one or more heteroatoms selected from N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. When the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results. Representative examples of heterocyclics include piperidinyl, piperazinyl, azepinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolidinyl, triazolyl, tetrazolyl, imidazolinyl, pyridyl (or pyridinyl), pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinoxalinyl, isothiazolidinyl, quinolinyl, isoquinolinyl, benzimidazolyl,

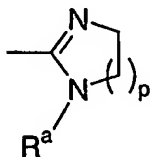
20

25

thiadazolyl, benzopyranyl, benzothiazolyl, benzoazolyl, furyl (or furanyl), tetrahydrofuryl (or tetrahydrofuranyl), tetrahydropuranyl, thienyl (alternatively thiophenyl), benzothiophenyl, oxadiazolyl, and benzo-1,3-dioxacyclopentyl (alternatively, 1,3-benzodioxolyl). Representative examples of heterocyclics also include tetrahydrothienyl, tetrahydrodioxothienyl, thiadiazinanyl, dioxothiadinanyl, thiazinanyl, dioxothiazinanyl, dioxothiazolidinyl, and isodioxothiazolidinyl. Representative examples of heterocyclics also include the following bicyclics: indolyl, benzotriazolyl, imidazo[4,5-b]pyridinyl, dihydroimidazo[4,5-b]pyridinyl, pyrazolo[4,3-c]pyridinyl, dihydropyrazolo[4,3-c]pyridinyl, tetrahydropyrazolo[4,3-c]pyridinyl, pyrrolo[1,2-a]pyrazinyl, dihydropyrrolo[1,2-a]pyrazinyl, tetrahydropyrrolo[1,2-a]pyrazinyl, octahydropyrrolo[1,2-a]pyrazinyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalanyl, quinazolinyl, cinnolinyl, chromanyl, and isochromanyl. Additional representative examples of bicyclics include the following: phthalazinyl, purinyl, 1,6-naphthyridinyl, 1,8-naphthyridinyl, dihydroindolyl, dihydroisoindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, imidazo[1,2-a]pyrimidinyl, 2,3-dihydroimidazo[2,1-b][1,3]thiazolyl, benzazepinyl, dihydrobenazepinyl, benzodiazepinyl, dihydrobenzodiazepinyl, and tetrahydrobenzodiazepinyl. Representative examples of heterocyclics also include the following tricyclics: phenothiazinyl, carbazolyl, beta-carbolinyl, tetrahydro-beta-carbolinyl, acridinyl, phenazinyl, and phenoxazinyl.

Representative examples of heterocyclics also include the following saturated monocyclics: hexahydropyrimidinyl, thiazinanyl (e.g., 1,2-thiazinanyl, alternatively named tetrahydro-1,2-thiazinyl), thiazepanyl (e.g., 1,4-thiazepanyl, alternatively named hexahydro-1,4-thiazepinyl), azepanyl (alternatively hexahydroazepinyl), thiadiazepanyl (e.g., 1,2,5-thiadiazepanyl), dithiazepanyl (e.g., 1,5,2-dithiazepanyl), diazepanyl (e.g., 1,4-diazepanyl), and thiadiazinanyl (e.g., 1,2,6-thiadiazinanyl).

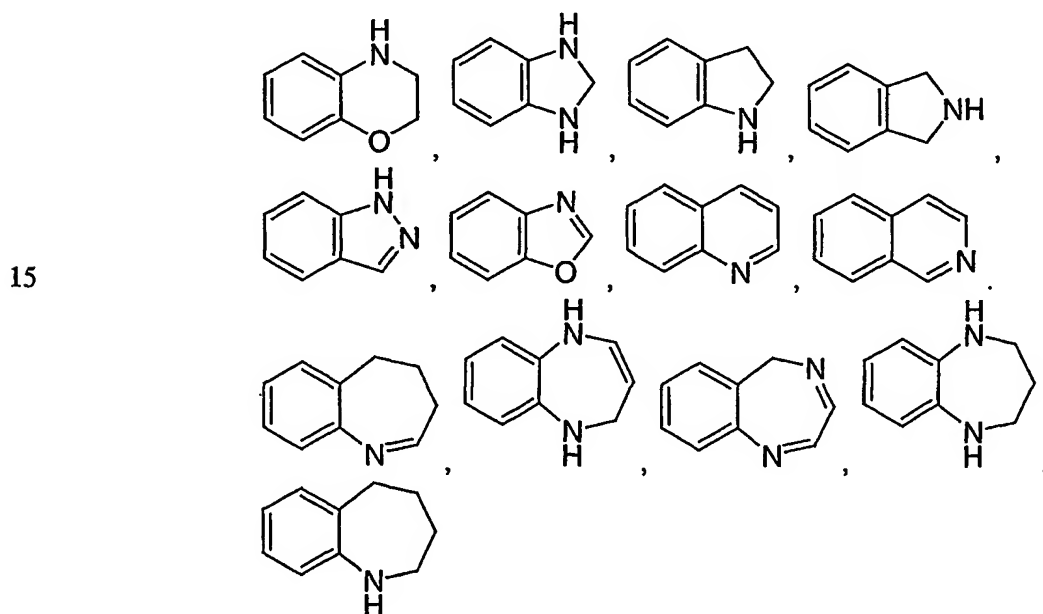
A representative unsaturated heterocycle, optionally substituted, is



, wherein p is an integer from zero to 4 and R^a is as defined above, and wherein each ring carbon is optionally and independently substituted with -C₁₋₄ alkyl.

Representative examples of heterocyclics also include the following bicyclics: hexahydropyrazolo[4,3-c]pyridinyl (e.g., 3a,4,5,6,7,7a-hexahydro-1H-pyrazolo[4,3c]pyridinyl), hexahydropurinyl (e.g., 2,3,4,5,6,7-hexahydro-1H-purinyl), hexahydrooxazolo[3,4a]pyrazinyl, and 1,2,3,4-tetrahydro-1,8-naphthyridinyl.

5 Fused ring heterocycles form a subset of the heterocycles as defined above; e.g., the term "fused bicyclic heterocycle" refers to a heteroatom-containing bicyclic ring system as defined in the preceding paragraph in which two adjacent atoms are shared by both rings. A subset of the fused bicyclic heterocycles is the fused bicyclic heterocycle containing carbon atoms and one or more heteroatoms
 10 selected from nitrogen, oxygen and sulfur, wherein one ring is a benzene ring and the other is a saturated or unsaturated heteroatom-containing ring. Representative examples of this subset include, but are not limited to, the following:



20 The term "heteromonocycle" (and variations thereof such as "heteromonocyclyl" or "heteromonocyclic") refers to a 4- to 8-membered monocyclic ring which is saturated or unsaturated, and which consists of carbon atoms and one or more heteroatoms selected from N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at

any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Representative examples of monoheterocycles are disclosed above.

Heteroaromatics form another subset of the heterocycles as defined above; i.e., the term "heteroaromatic" (alternatively, "heteroaryl") generally refers to a heterocycle as defined above in which the ring system (whether mono- or poly-cyclic) is an aromatic ring system. The term "heteroaromatic ring" refers to a monocyclic heterocycle as defined above which is an aromatic heterocycle. Representative examples of heteroaromatics include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl.

Unless expressly set forth to the contrary, an "unsaturated" ring is a partially or fully unsaturated ring. For example, an "unsaturated monocyclic C₆ carbocycle" refers to cyclohexene, cyclohexadiene, and benzene.

The present invention includes pharmaceutical compositions useful for inhibiting HIV integrase, comprising an effective amount of a compound of this invention, and a pharmaceutically acceptable carrier. Pharmaceutical compositions useful for treating infection by HIV, or for treating AIDS or ARC, are also encompassed by the present invention, as well as a method of inhibiting HIV integrase, and a method of treating infection by HIV, or of treating AIDS or ARC. Additionally, the present invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of an agent for treating HIV infection or AIDS selected from:

- (1) an antiviral agent useful for treating or preventing HIV infection or for treating AIDS (also referred to herein as an HIV/AIDS antiviral agent),
- (2) an anti-infective agent, and
- (3) an immunomodulator.

The present invention also includes a compound of the present invention for use in (a) inhibiting HIV protease, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS or ARC. The present invention also includes the use of a compound of the present invention as described above as a medicament for (a) inhibiting HIV integrase, (b) preventing or treating

infection by HIV, or (c) preventing, treating or delaying the onset of AIDS or ARC. The present invention further includes the use of any of the HIV integrase inhibiting compounds of the present invention as described above in combination with one or more HIV/AIDS treatment agents selected from an HIV/AIDS antiviral agent, an anti-infective agent, and an immunomodulator as a medicament for (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS or ARC, said medicament comprising an effective amount of the HIV integrase inhibitor compound and an effective amount of the one or more treatment agents.

10 The present invention also includes the use of a compound of the present invention as described above in the preparation of a medicament for (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS or ARC.

15 The present invention further includes the use of any of the HIV integrase inhibiting compounds of the present invention as described above in combination with one or more HIV/AIDS treatment agents selected from an HIV/AIDS antiviral agent, an anti-infective agent, and an immunomodulator for the manufacture of a medicament for (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS or ARC, said medicament comprising an effective amount of the HIV integrase inhibitor compound and an effective amount of the one or more treatment agents.

20 The compounds of the present invention may have asymmetric centers and may occur, except when specifically noted, as mixtures of stereoisomers or as individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

25 When any variable (e.g., R^a, R^b, R^c, R^k, etc.) occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

30 The term "substituted" (e.g., as in "phenyl ring, unsubstituted or substituted with from 1 to 5 substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution is chemically

allowed. For example, a carbocycle or heterocycle substituted with more than one substituent can have multiple substituents on the same ring atom to the extent it is chemically permitted. A ring sulfur atom in a saturated heterocycle can, for example, typically be substituted with 1 (-S(=O)-) or 2 oxo groups (-SO₂-).

5 The compounds of the present inventions are useful in the inhibition of HIV integrase, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS
10 related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by e.g., blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

15 The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the
20 binding site of other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

 The present invention also provides for the use of a compound of Formula (I) to make a pharmaceutical composition useful for inhibiting HIV integrase
25 and in the treatment of AIDS or ARC.

 The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" is intended to include all acceptable salts such as acetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate,
30 mandelate, bitartrate, mesylate, borate, methylbromide, bromide, methylnitrate, calcium edetate, methylsulfate, camsylate, mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate (embonate), estolate, palmitate, esylate, pantothenate, fumarate, phosphate/diphosphate, gluceptate, polygalacturonate,

gluconate, salicylate, glutamate, stearate, glycolylarsanilate, sulfate, hexylresorcinate, subacetate, hydrabamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate, isothionate, triethiodide, lactate, pantoate, valerate, and the like which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-drug formulations. Depending on the particular functionality of the compound of the present invention, pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylene-diamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethyl-amine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide. These salts may be prepared by standard procedures, e.g. by reacting a free acid with a suitable organic or inorganic base. Where a basic group is present, such as amino, an acidic salt, i.e. hydrochloride, hydrobromide, acetate, pantoate, and the like, can be used as the dosage form.

Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed, e.g. acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

For these purposes, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention each mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HIV infection or AIDS), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or prodrug thereof and other agents.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a subject in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and
5 a therapeutically-effective amount of a compound of the present invention.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

10 By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term "subject," (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who
15 has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes
20 alleviation of the symptoms of the disease being treated.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets or capsules, nasal sprays, sterile injectible preparations, for example, as sterile injectible aqueous or oleagenous suspensions or suppositories.

25 When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these
30 compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical

formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

5 The injectible solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

10 When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

15 The compounds of this invention can be administered orally to humans in a dosage range of 0.1 to 1000 mg/kg body weight in divided doses. One preferred dosage range is 0.1 to 200 mg/kg body weight orally in divided doses. Another preferred dosage range is 0.5 to 100 mg/kg body weight orally in divided doses. For oral administration, the compositions are preferably provided in the form of tablets
20 containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. It will be understood, however, that the specific dose level and frequency of dosage for any
25 particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

30 The present invention is also directed to combinations of the HIV integrase inhibitor compounds with one or more agents useful in the treatment of HIV infection or AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the HIV/AIDS antivirals, immunomodulators,

antiinfectives, or vaccines useful for treating HIV infection or AIDS, such as those in the following Table.

ANTIVIRALS

5

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Amprenavir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir GW 1592 1592U89	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil	Gilead Sciences	HIV infection
AL-721	Ethigen (Los Angeles, CA)	ARC, PGL, HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV, in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which neutralizes pH labile alpha aberrant Interferon AR177	Advanced Biotherapy Concepts (Rockville, MD) Aronex Pharm	AIDS, ARC HIV infection, AIDS, ARC

beta-fluoro-ddA BMS-232623 (CGP-73547)	Nat'l Cancer Institute Bristol-Myers Squibb/ Novartis	AIDS-associated diseases HIV infection, AIDS, ARC (protease inhibitor)
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012 Cidofovir	Warner-Lambert Gilead Science	HIV-1 infection CMV retinitis, herpes, papillomavirus
Curdlan sulfate Cytomegalovirus immune globin	AJI Pharma USA MedImmune	HIV infection CMV retinitis
Cytovene Ganciclovir	Syntex	sight threatening CMV peripheral CMV retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine ddI Dideoxyinosine	Hoffman-La Roche Bristol-Myers Squibb	HIV infection, AIDS, ARC combination with AZT/d4T
mozenavir (DMP-450)	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection

Efavirenz (DMP 266) (-) 6-Chloro-4(S)- cyclopropylethynyl- 4(S)-trifluoro-methyl- 1,4-dihydro-2H-3,1- benzoxazin-2-one,	DuPont (SUSTIVA®), Merck (STOCRIN®)	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBV097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
Compound A	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases

Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boehringer Ingleheim	HIV infection, AIDS, ARC (protease inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
Ritonavir (ABT-538)	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy- thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	genital HSV & CMV infections
Virazole	Viratek/ICN	asymptomatic HIV
Ribavirin	(Costa Mesa, CA)	positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC

Zalcitabine	Hoffmann-La Roche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma in combination with other therapies (reverse transcriptase inhibitor)
ABT-378; Lopinavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
ABT-378/r; contains lopinavir and ritonavir; Kaletra	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
JE2147/AG1776	Agouron	HIV infection, AIDS, ARC (protease inhibitor)
T-20	Trimeris	HIV infection, AIDS, ARC (fusion inhibitor)
T-1249	Trimeris	HIV infection, AIDS, ARC (fusion inhibitor)
atazanavir (BMS 232632)	Bristol-Myers-Squibb	HIV infection, AIDS, ARC (protease inhibitor)
PRO 542	Progenics	HIV infection, AIDS, ARC (attachment inhibitor)
PRO 140	Progenics	HIV infection, AIDS, ARC (CCR5 co-receptor inhibitor)
TAK-779	Takeda	HIV infection, AIDS, ARC (injectable CCR5 receptor antagonist)
DPC 681 & DPC 684	DuPont	HIV infection, AIDS, ARC (protease inhibitors)
DPC 961 & DPC 083	DuPont	HIV infection AIDS, ARC (nonnucleoside reverse transcriptase inhibitors)

Trizivir (contains abacavir, lamivudine, and zidovudine)	GlaxoSmithKline	HIV infection, AIDS, ARC (reverse transcriptase inhibitors)
tipranavir (PNU-140690)	Boehringer Ingelheim (purchased from Pharmacia & Upjohn)	HIV infection, AIDS, ARC (protease inhibitor)
tenofovir disoproxil fumarate	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
TMC-120 & TMC-125	Tibotec	HIV infections, AIDS, ARC (non-nucleoside reverse transcriptase inhibitors)
TMC-126	Tibotec	HIV infection, AIDS, ARC (protease inhibitor)

IMMUNO-MODULATORS

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)

Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	seropositive HIV
IL-2	Cetus	AIDS, in combination w/AZT
Interleukin-2		
IL-2	Hoffman-La Roche	AIDS, ARC, HIV, in combination w/AZT
Interleukin-2	Immunex	
IL-2	Chiron	AIDS, increase in CD4 cell counts
Interleukin-2 (aldeslukin)		
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC

MTP-PE	Ciba-Geigy Corp.	Kaposi's sarcoma
Muramyl-Tripeptide		
Granulocyte	Amgen	AIDS, in combination
Colony Stimulating		w/AZT
Factor		
Remune	Immune Response Corp.	immunotherapeutic
rCD4	Genentech	AIDS, ARC
Recombinant		
Soluble Human CD4		
rCD4-IgG		AIDS, ARC
hybrids		
Recombinant	Biogen	AIDS, ARC
Soluble Human CD4		
Interferon	Hoffman-La Roche	Kaposi's sarcoma, AIDS,
Alfa 2a		ARC, in combination w/AZT
SK&F106528	Smith Kline	HIV infection
Soluble T4		
Thymopentin	Immunobiology	HIV infection
	Research Institute	
Tumor Necrosis	Genentech	ARC, in combination
Factor; TNF		w/gamma Interferon
etanercept	Immunex Corp	rheumatoid arthritis
	(Enbrel®)	
infliximab	Centocor (Remicade®)	rheumatoid arthritis and
		Crohn's disease

ANTI-INFECTIVES

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Clindamycin with	Pharmacia Upjohn	PCP
Primaquine		
Fluconazole	Pfizer	cryptococcal meningitis,
		candidiasis

Pastille	Squibb Corp.	prevention of oral candidiasis
Nystatin Pastille		
Ornidyl	Merrell Dow	PCP
Eflornithine		
Pentamidine	LyphoMed	PCP treatment
Isethionate (IM & IV)	(Rosemont, IL)	
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine	Fisons Corporation	PCP prophylaxis
isethionate for inhalation		
Spiramycin	Rhone-Poulenc	cryptosporidia diarrhea
Intraconazole-	Janssen Pharm.	histoplasmosis; cryptococcal
R51211		meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Daunorubicin	NeXstar, Sequus	Karposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Leukotriene B4 Receptor Antagonist	-	HIV infection
Megestrol Acetate	Bristol-Myers Squibb	treatment of anorexia assoc. w/AIDS
Soluble CD4 Protein and Derivatives	-	HIV infection
Testosterone	Alza, Smith Kline	AIDS-related wasting

Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	diarrhea and malabsorption, related to AIDS
----------------------------	----------------------------------	--

It will be understood that the scope of combinations of the compounds of this invention with HIV/AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of HIV infection or AIDS. When employed in combination with the compounds of the invention, the HIV/AIDS antivirals and other agents are typically employed in their conventional dosage ranges and regimens as reported in the art, including the dosages described in the Physicians' Desk Reference, 54th edition, Medical Economics Company, 2000. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above just before the Table.

Preferred combinations are simultaneous or sequential treatments of a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is the sulfate salt of indinavir, which is N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to US 5413999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Still another preferred protease inhibitor is Compound A, which is N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(2-benzo[b]furanylmethyl)-2(S)-N'-(t-butylcarboxamido)piperazinyl))pentaneamide, preferably administered as the sulfate salt. Compound A can be prepared as described in US 5646148. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV.

Preferred combinations include a compound of the present invention with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI

and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine.

5 Another preferred combination is a compound of the present invention with indinavir and Compound A and optionally with one or more of efavirenz, AZT, 3TC, ddI and ddC. In one embodiment of this combination, the weight ratio of indinavir to Compound A is from about 1:1 to about 1:2, wherein the amount of indinavir employed is in the range of from about 200 to about 1000 mg. Indinavir and
10 Compound A can be administered concurrently or sequentially in either order from one to three times per day.

 In such combinations the compound of the present invention and other active agents may be administered together or separately. In addition, the administration of one agent may be prior to, concurrent to, or subsequent to the
15 administration of other agent(s).

 Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

 DEAD = diethylazodicarboxylate
 DMF = N,N-dimethylformamide
20 DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
 DMSO = dimethylsulfoxide
 EDC = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
 ES MS = electrospray mass spectrometry
 Et = ethyl
25 FAB MS = fast atom bombardment mass spectrometry
 HPLC = high performance liquid chromatography
 HOBt = 1-hydroxy benzotriazole hydrate
 HPLC = high performance liquid chromatography
 i-Pr = isopropyl
30 Me = methyl

MsCl = methanesulfonyl chloride (or mesyl chloride)

NBS = N-bromosuccinimide

NIS = N-iodosuccinimide

NMR = nuclear magnetic resonance

5 Ph = phenyl

PMBCl = *p*-methoxybenzyl chloride

NMR = nuclear magnetic resonance

rt and RT = room temperature

TFA = trifluoroacetic acid

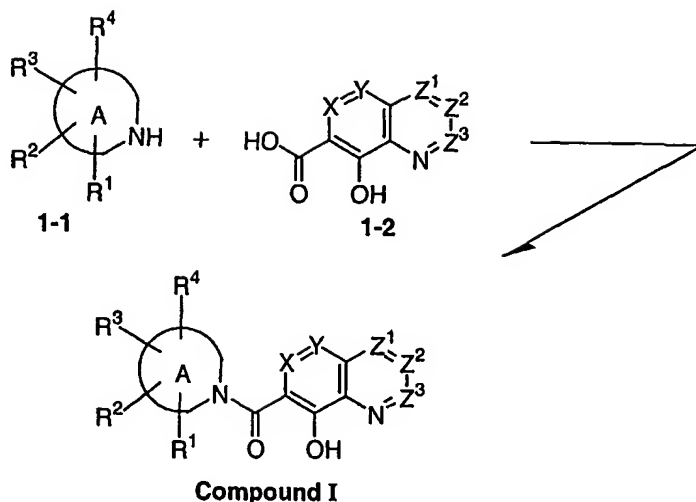
10 THF = tetrahydrofuran

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

The compounds of the present invention can be prepared by the coupling of suitable (poly)azanaphthenyl carboxylic acids (or acid derivatives such as acid halides or esters) with the appropriate amines, as represented by the following general scheme:

25

SCHEME 1



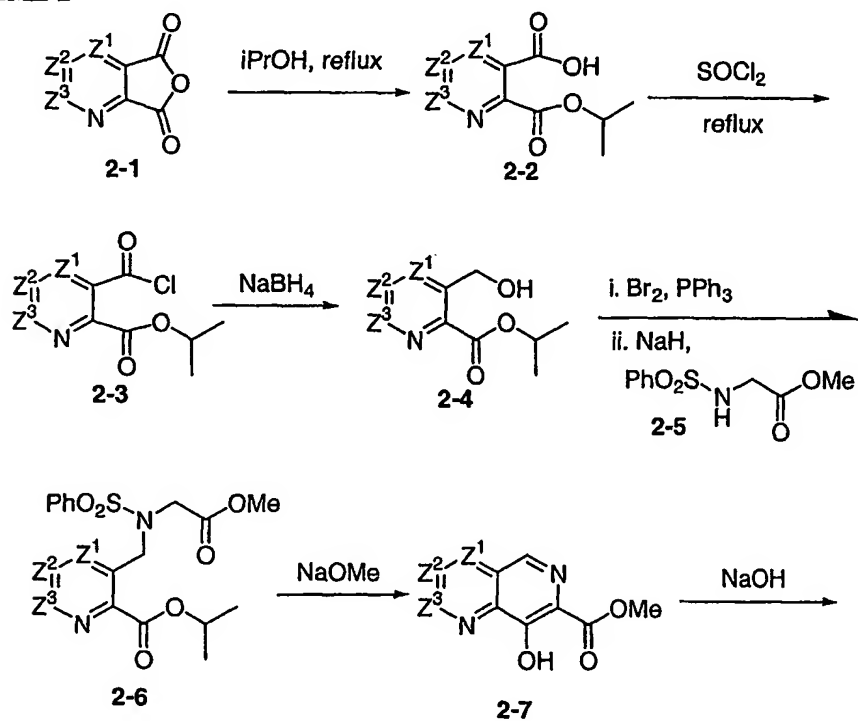
Methods for coupling carboxylic acids with amines to form carboxamides are well known in the art. Suitable methods are described, for example, in Jerry March, *Advanced Organic Chemistry*, 3rd edition, John Wiley & Sons, 1985, pp. 370-376. Amines of formula 1-1 can be prepared using the methods described in Richard Larock, *Comprehensive Organic Transformations*, VCH Publishers Inc, 1989, pp 385-438, or routine variations thereof. Azanaphthenyl and polyazanaphthenyl carboxylic acids of formula 1-2 can be prepared using methods described in Ochiai et al., *Chem.Ber.* 1937, 70: 2018, 2023; Albert et al., *J.Chem.Soc.* 1952, 4985, 4991; and Barlin et al., *Aust.J.Chem.* 1990, 43: 1175-1181; or routine variations thereof. Schemes 2-16 below illustrate and expand upon the chemistry portrayed in Scheme 1.

In Scheme 2, following the procedure set forth in Ornstein et al., *J. Med. Chem.* 1989, 32: 827-833, a cyclic anhydride such as quinolinic anhydride (i.e., $Z^1 = Z^2 = Z^3 = \text{CH}$ in 2-1) can be opened with isopropanol to provide mono acid 2-2, which can be converted to the corresponding acyl chloride 2-3 (e.g., by refluxing thionyl chloride). Acyl chloride 2-3 can then be reduced (e.g., with NaBH_4 or LiBH_4) to the corresponding alcohol 2-4, which can be converted to the corresponding bromide through the action of bromine in the presence of triphenylphosphine. Alkylation of the bromide with the sodium anion of phenylsulfonamide 2-5 in a polar aprotic solvent like DMF can provide sulfonamide 2-6, which can be treated with a base (e.g., alkali metal alkoxide such as sodium methoxide) to provide the bicyclic ester 2-7 via a Dieckmann cyclization.

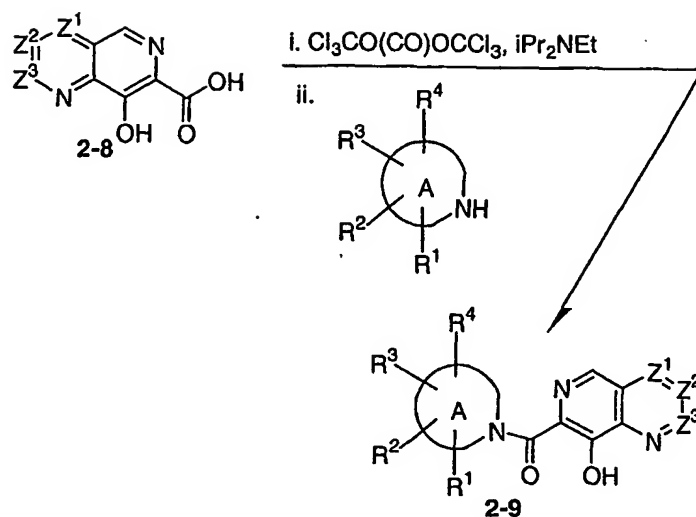
Saponification of the ester (e.g., with aqueous NaOH at reflux) will afford the acid **2-8**. The acid **2-8** can be activated with triphosgene and coupled with a variety of amines to provide the compounds of the invention **2-9**.

The starting anhydrides of formula **2-1** can be prepared via methods described in Philips et al., *Justus Liebigs Ann. Chem.* 1895, 288: 2535; Bernthsen et al., *Chem. Ber.* 1887; 20: 1209; Bly et al., *J. Org. Chem.* 1964, 29: 2128-2135; and Krapcho et al., *J. Heterocycl. Chem.* 1993, 30: 1597-1606; or routine variations thereof.

10 SCHEME 2

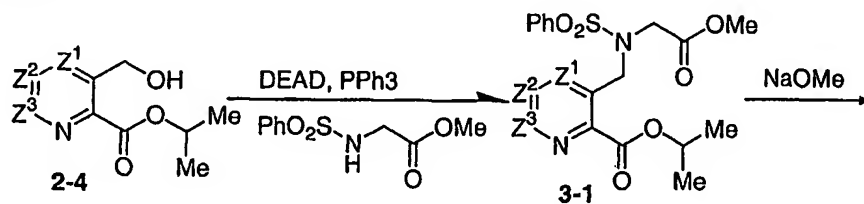


15

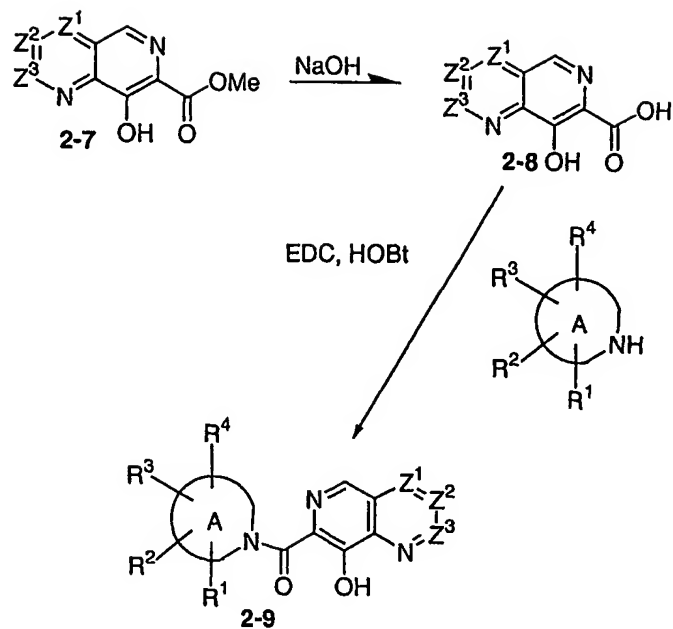


Scheme 3 depicts an alternative synthesis in which alcohol **2-4** can undergo the Mitsunobu reaction with the phenylsulfonamide of glycine methyl ester to provide **3-1**. The sulfonamide **3-1** can again be elaborated to provide the acid **2-8**, which can be coupled with a variety of amines using standard reagents to provide the compounds of the invention **2-9**.

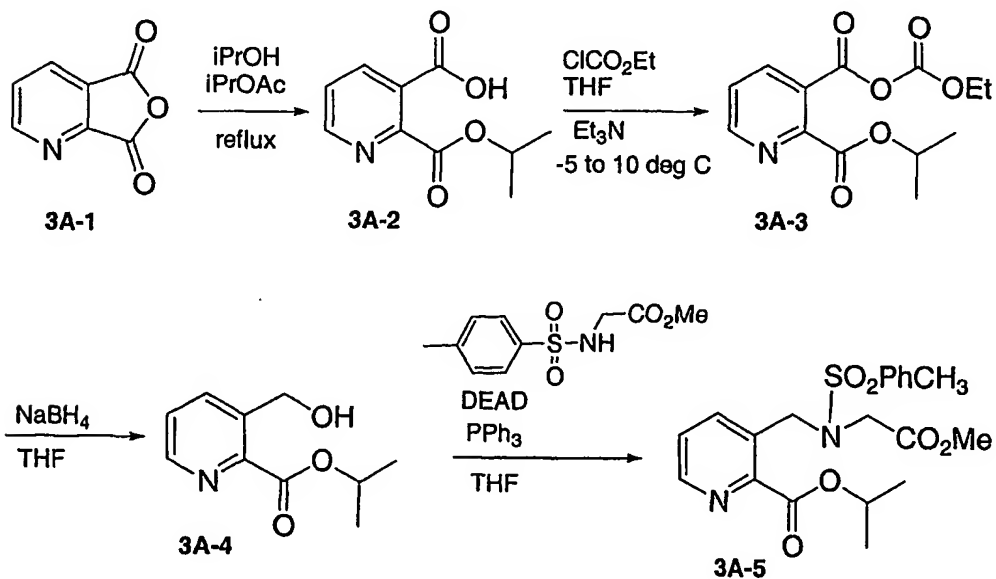
SCHEME 3

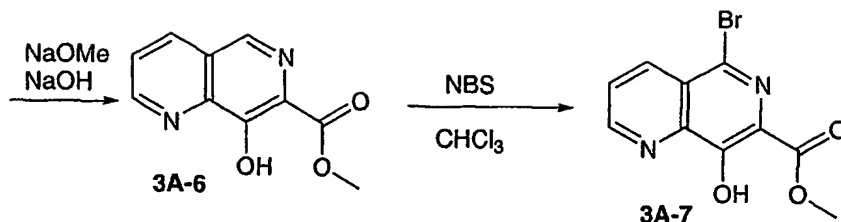


10



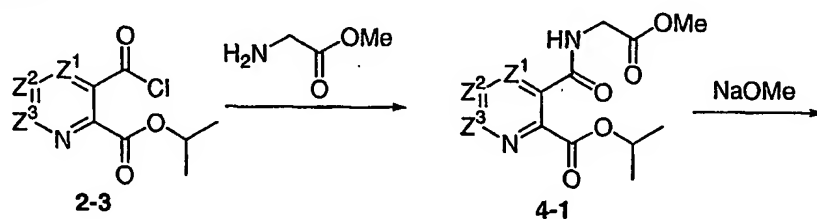
Scheme 3A depicts (for a naphthyridine core) a variation of the synthesis shown in Scheme 3, wherein the acid 3A-2 is reacted with ethyl chloroformate to form the mixed anhydride 3A-3, which is reduced to alcohol 3A-4.

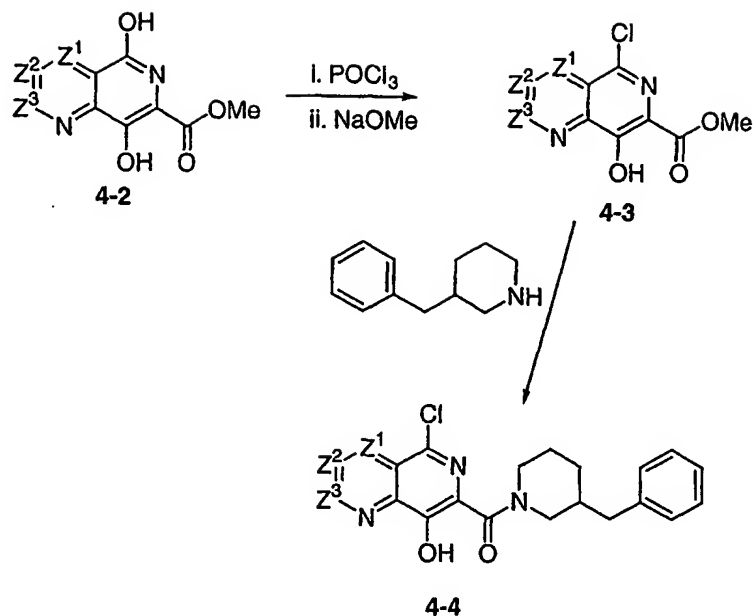




Halogen substituted compounds of the present invention can be prepared as shown in Scheme 4. The acid chloride **2-3** can be reacted with glycine methyl ester to provide the amide **4-1**. Dieckmann cyclization of the ester **4-1** with a sodium alkoxide base in an alcoholic solvent like methanol will provide phenol **4-2**, which can be reacted with phosphorous oxychloride, followed by methanolysis of the intermediate phosphonate esters to provide **4-3**. The ester bond of **4-3** can react selectively with suitable amines (e.g., 3-benzylpiperidine is depicted in Scheme 4) to provide the corresponding halogenated derivative **4-4**.

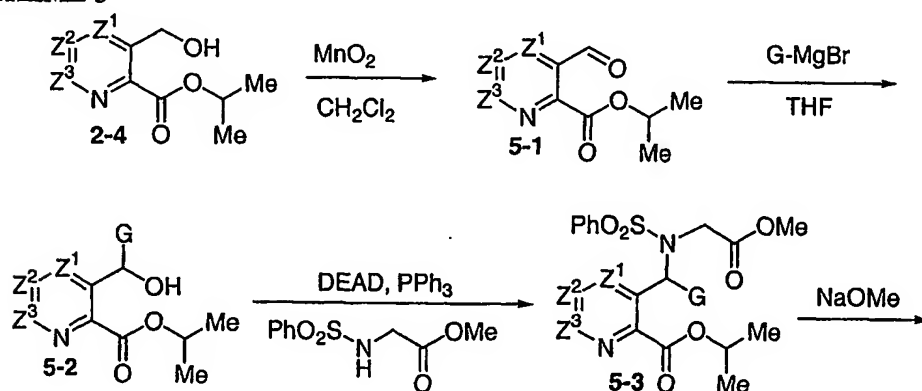
SCHEME 4

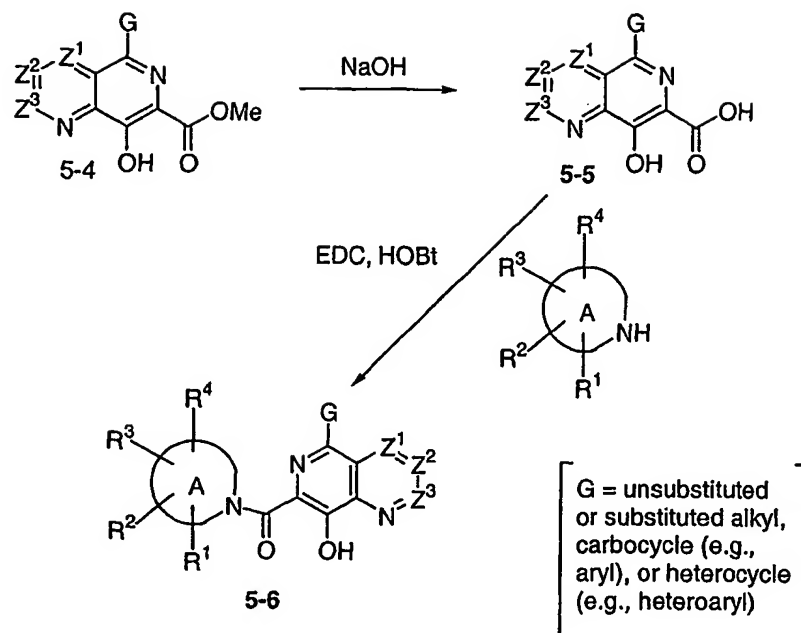




The preparation of compounds that feature additional substituents can be achieved as shown in Scheme 5. Oxidation of the alcohol **2-4** with manganese dioxide in an inert solvent such as methylene chloride will provide aldehyde **5-1**. The addition of Grignard reagents (such as phenyl magnesium bromide) to aldehyde moiety **5-1** can occur regioselectively to provide the alcohol **5-2**, which can then be elaborated to the compounds of the invention **5-6**.

10 SCHEME 5

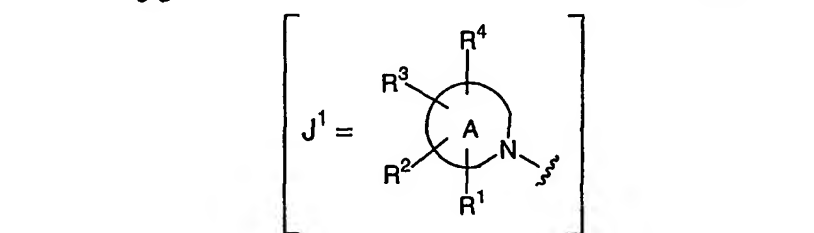
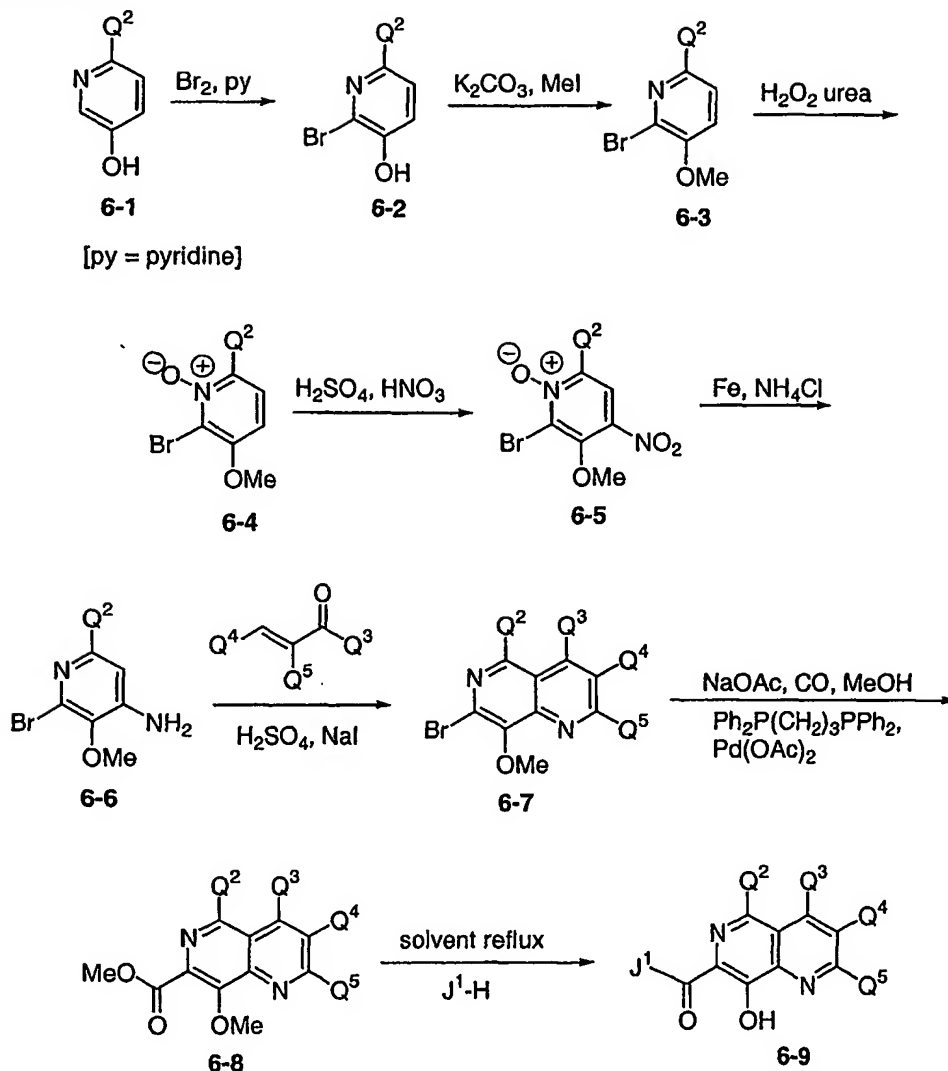




A further synthetic route to prepare compounds that are the subject of the invention is shown in Scheme 6. This methodology allows access to naphthyridine derivatives that are substituted at the 2, 3, 4 and 5 positions. Briefly, a 2-substituted 5-hydroxypyridine derivative **6-1** can be treated with bromine to undergo bromination at the 6 position to afford **6-2**, which can be converted to the methoxypyridine **6-3** and then oxidized to the corresponding N-oxide **6-4**. The N-oxide can be nitrated to provide **6-5**. Reduction of **6-5** with iron in the presence of ammonium chloride can provide the aniline **6-6**, which can be reacted with an alpha,beta-unsaturated aldehyde or ketone in the presence of an acid catalyst like sulfuric acid to provide **6-7** via an annulation. The bromide **6-7** can be elaborated to the amide **6-9** via a sequence of carbonylation and amidation reactions.

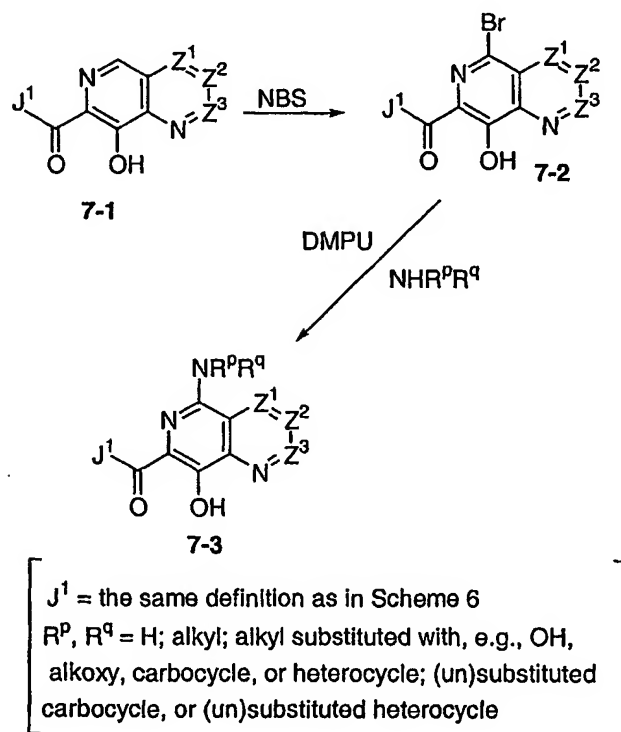
2-Substituted 5-hydroxypyridine derivatives of formula **6-1** can be prepared via methods described in Sorm et al., *Collect.Czech.Chem..Commun.*1949, 14: 331,342; and Saksena et al., *Tetrahedron Lett.*1993, 34: 3267-3270; or routine variations thereof.

SCHEME 6

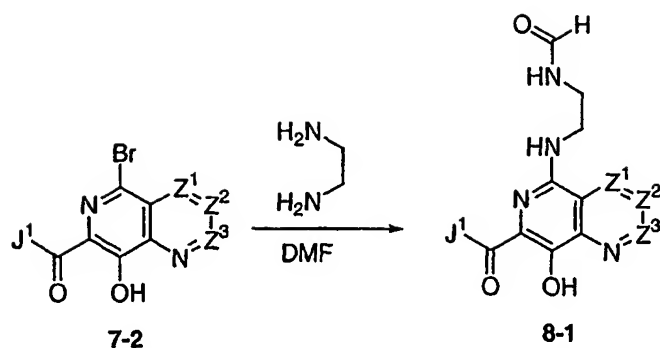


Compounds of the invention that comprise an amino substituent at the 5 position can be prepared in the manner set forth in Schemes 7 and 8. Bromination of the phenol 7-1 occurs regioselectively upon treatment with NBS in an inert solvent like methylene chloride to afford 7-2. Reaction of this bromide with an amine at elevated temperatures in the presence of a polar solvent such as DMPU affords compounds of the invention 7-3. Similar reaction of the bromide 7-2 (Scheme 8) with a diamine such as ethylene diamine in DMF as solvent will afford the formylated derivative 8-1 in addition to the expected diaminoethane derivative.

10 SCHEME 7

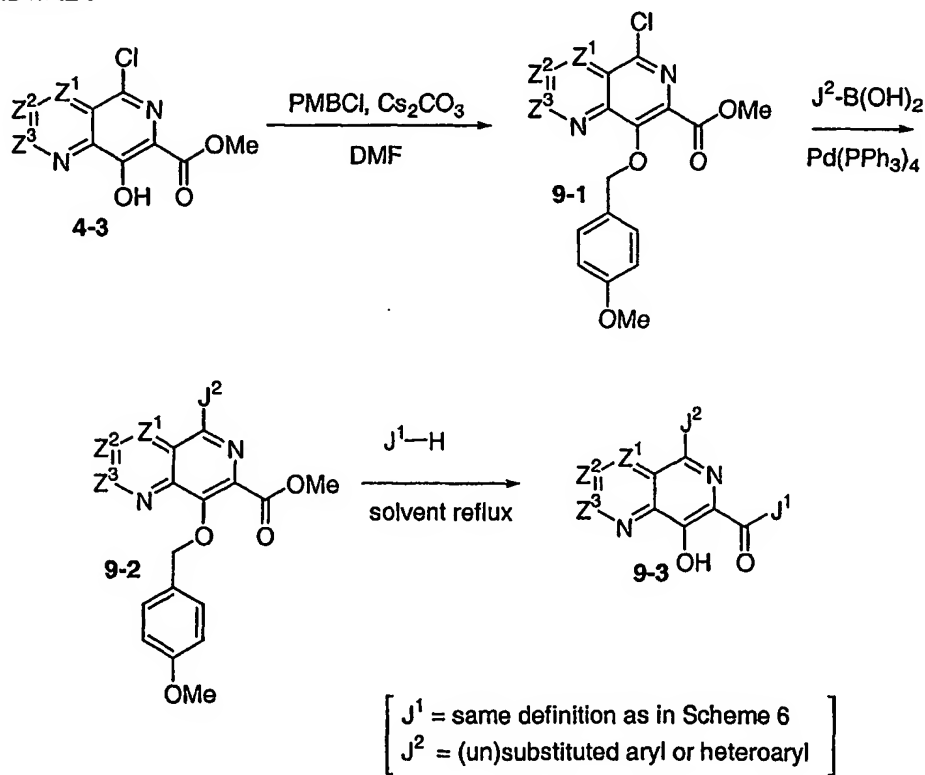


SCHEME 8



Preparation of aryl and heteroaryl derivatives via palladium cross
 5 coupling of the chloride 9-1 and the requisite boronic acids are depicted in Scheme 9.

SCHEME 9

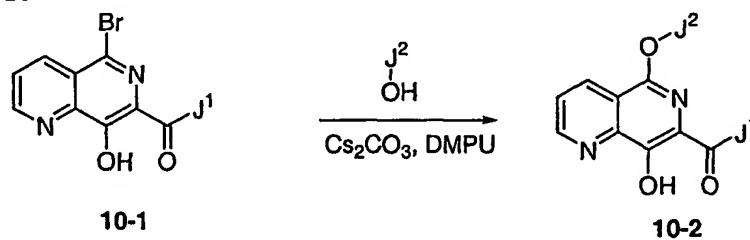


10

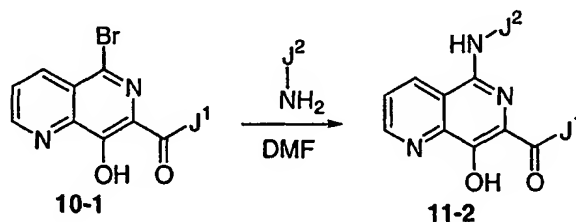
(Hetero)aryloxy, (hetero)arylamino, and (heteroaryl)thioxy derivatives
 10-2, 11-2, and 12-2 respectively can be prepared as shown in Schemes 10 to 12,

which exemplify the procedure for the naphthyridine core. The corresponding sulfone derivatives **12-2** can be obtained by oxidation of the sulfides **12-1** with either ozone or 3-chloroperbenzoic acid as shown in Scheme 12.

5 SCHEME 10

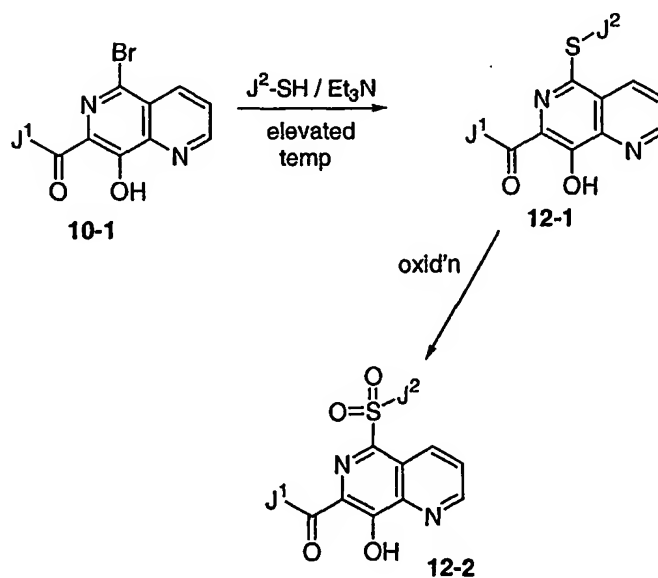


SCHEME 11



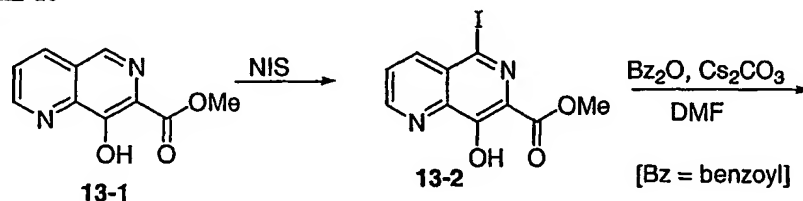
10

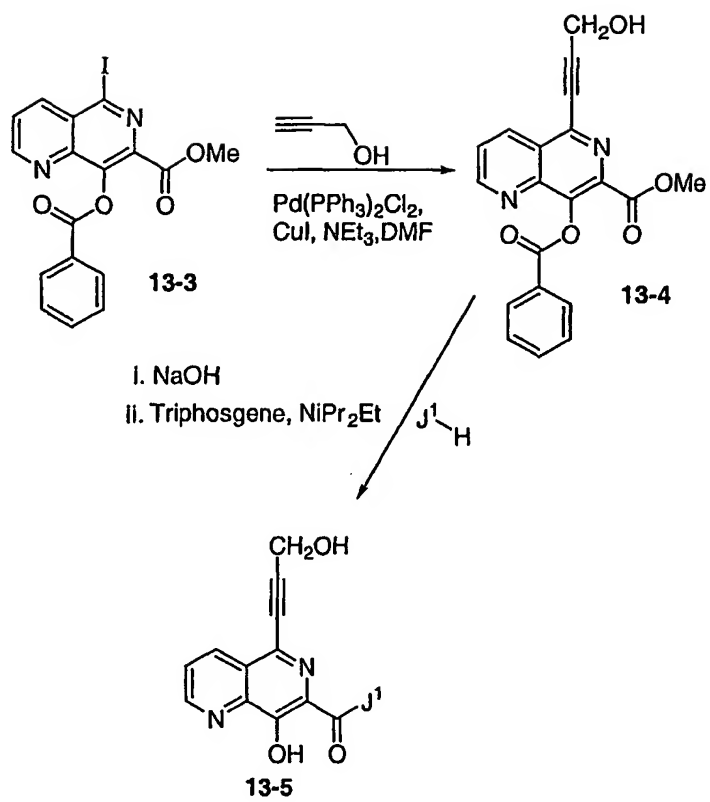
SCHEME 12



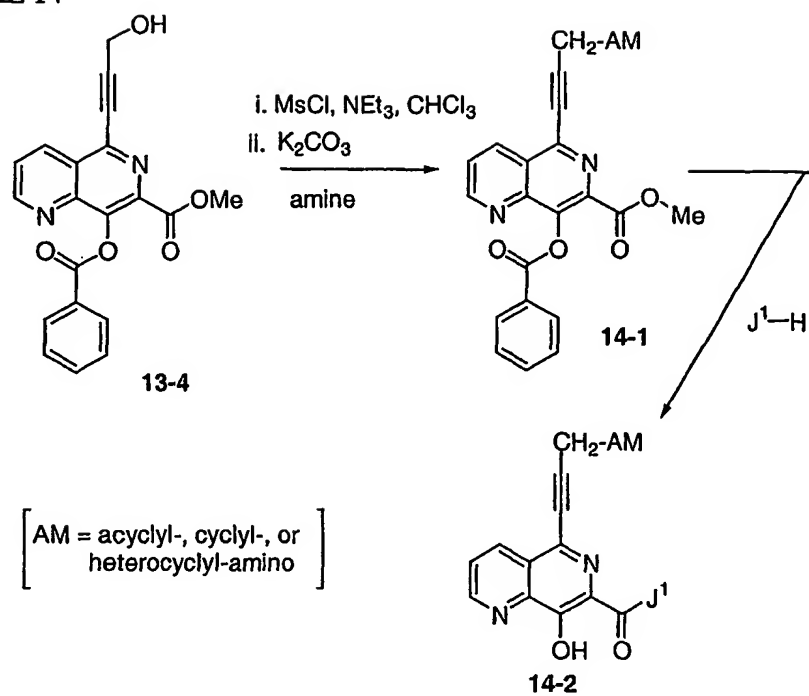
Preparation of compounds of the invention substituted with an acetylene can be prepared according to Scheme 13, which exemplifies the procedure for the naphthyridine core. Following protection of the iodide **13-2** as its benzoate **13-3**, the acetylenic group (for example propynol) can be appended by employing a suitable palladium catalyst in the presence of copper iodide. Aminolysis of the ester **13-4** will afford the amide **13-5** with concomitant deprotection of the benzoate ester. Alternately the ester **13-4** can be converted to the corresponding amine and sulfone derivatives as shown in Schemes 14 and 15. Scheme 16 shows that the preparation of the nitrile derivative **16-2** can be achieved via a palladium catalyzed cyanation of the iodide **13-4**.

SCHEME 13

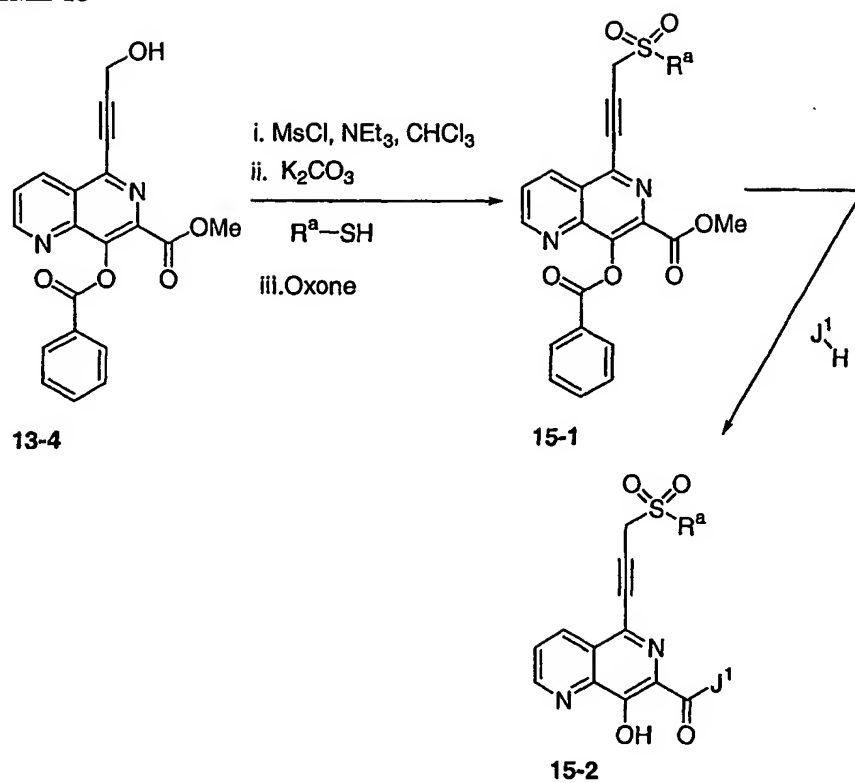




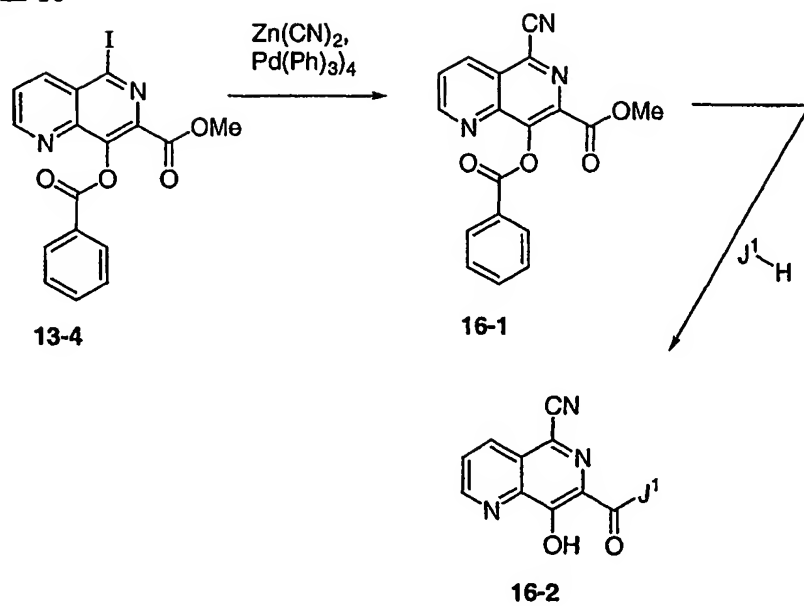
SCHEME 14



SCHEME 15



SCHEME 16

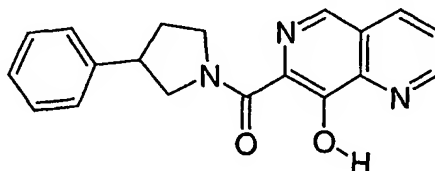


In the processes for preparing compounds of the present invention set forth in the foregoing schemes, functional groups in various moieties and substituents may be sensitive or reactive under the reaction conditions employed and/or in the presence of the reagents employed. Such sensitivity/reactivity can interfere with the progress of the desired reaction to reduce the yield of the desired product, or possibly even preclude its formation. Accordingly, it may be necessary or desirable to protect sensitive or reactive groups on any of the molecules concerned. Protection can be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973 and in T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art. Alternatively the interfering group can be introduced into the molecule subsequent to the reaction step of concern. For example, if one or more of the substituents R¹, R², R³, and R⁴ in compound 1-1 can interfere with the coupling reaction between compounds 1-1 and 1-2 of Scheme 1, the substituent can be incorporated into the molecule in a post-coupling step to afford Compound I.

The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLE 1

7-[(3-phenylpyrrolidin-1-yl)carbonyl]-1,6-naphthyridin-8-ol



Step 1: Preparation of 3-([Methoxycarbonylmethyl-(toluene-4-sulfonyl)-amino]-methyl)-pyridine-2-carboxylic acid isopropyl ester
Isopropyl 3-(hydroxymethyl)pyridine-2-carboxylate (prepared in accordance with P. Ornstein et. al. *J. Med. Chem.* 1989, 32, 827) (200g, 1.02 mol),

methyl N-[(4-methylphenyl)sulfonyl]glycinate (249g, 1.02 mol), and triphenylphosphine (403g, 1.5 mol) were dissolved in dry THF (3000mls) and cooled to zero degrees under N₂. The diethylazodicarboxylate (DEAD) (267.6 g, 1.5 mol) was dissolved in dry THF (250 mls) and placed in a 500 ml addition funnel. The
5 DEAD was added dropwise over 1 hour. The ice bath was removed and the reaction was allowed to warm slowly to RT. After 2 hours, the reaction was checked by HPLC (above conditions) and some glycinate remained. More starting reagents were added and the reaction was left to stir at RT. After 30 min, the reaction was checked again and saw a very small amount of the glycinate remaining. Concentrated reaction
10 down to a reddish-orange oil that was carried onto the next step.

Step 2: Preparation of methyl 8-hydroxy-1,6-naphthyridine-7-carboxylate
3-[[Methoxycarbonylmethyl-(toluene-4-sulfonyl)-amino]-methyl]-pyridine-2-carboxylic acid isopropyl ester (1.02 mol) was dissolved in dry methanol
15 (4000ml) and cooled to zero degrees under nitrogen. Then via addition funnel, sodium methoxide (137.8g, 2.5 mol) was added slowly to avoid any exotherm. The reaction was stirred at zero degrees, and checked by HPLC after 1.5 hours and was found to be completed. The solvent was removed *in vacuo* to obtain a reddish-orange oil, which was partitioned between water (1L) and ethyl acetate (1L). The organic
20 layer was back extracted with saturated sodium bicarbonate solution. The pH of the aqueous layer was adjusted to 7, and the layer was maintained at this pH while extracting with methylene chloride. The organic layer was dried with Na₂SO₄, filtered, and the solvent was removed *in vacuo* to obtain a tan solid. The solid was dissolved in hot ethyl acetate, and the solution was filtered while hot to filter out any
25 insoluble material. The product precipitated upon cooling. The precipitate was then filtered and dried in a vacuum oven. The filtrate was recrystallized by concentrating the filtrate and redissolving the resulting solid in a minimal amount of methylene chloride. Sufficient ethyl acetate was added to turn the solution slightly cloudy, after which the solution was boiled to reduce the volume, cooled, and the resulting crystals
30 were filtered out and dried in a vacuum oven.

¹H NMR (CDCl₃, 500MHz) δ 11.79 (5H, s), 9.20 (1H, dd, *J*= 1.7 and 6.1Hz), 8.80 (1H, s), 8.30 (1H, dd, *J*=1.5 and 9.7 Hz), 7.70 (1H, dd, *J*= 4.2 and 12.4 Hz) and 4.10 (3H,s) ppm.

ES MS exact mass calculated for C₁₀H₈N₂O₃ 204.1869 (MH⁺), found 205.1.

Step 3: Preparation of 8-hydroxy-1,6-naphthyridine-7-carboxylic acid

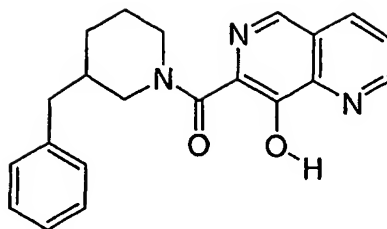
- To a slurry of methyl 8-hydroxy-1,6-naphthyridine-7-carboxylate from Example 1, Step 2 (1.50g, 7.35 mmol) in methanol (45ml) was added lithium hydroxide (22.0ml of a 1M aq. solution, 22.0 mmol) and the reaction was heated at 100°C for 7 hrs. Upon cooling to room temperature, hydrochloric acid (22.0ml of a 1M aq. solution, 22.0 mmol) was added and the reaction stirred for 16 hrs. The mixture was concentrated to a volume of 50 ml and neutralized with dilute NaHCO₃ (pH=7). The resulting precipitate was collected by filtration and washed with water and dried *in vacuo* to afford the title compound.
- FAB MS calcd for C₉H₆N₂O₃ 191 (MH⁺), found 191.
- ¹H NMR (d₆DMSO, 400MHz) δ 9.20 (1H, m), 8.72 (1H, s), 8.58 (1H, m), 7.80 (1H, dd, J=8.3 and 4.2 Hz) ppm.

Step 4: Preparation of 7-[(3-phenylpyrrolidin-1-yl)carbonyl]-1,6-naphthyridin-8-ol

- Triphosgene (0.556g, 1.87 mmol) was added over 20 mins to a solution of the acid from Step 3. (0.89g, 4.68 mmol) and diisopropylethylamine 3.26 ml, 18.7 mmol) in DMF (22 ml) at 0°C. The dark solution was allowed to warm to room temperature and stirred a further 1 hr. 3-phenylpyrrolidine (15.46 mg, 1.05 mmol) was treated with a portion of the above solution (0.58ml, 0.07 mmol) and the resulting mixture was stirred at room temperature for 16 hrs. The solution was treated with trifluoroacetic acid (TFA) (0.025 ml) and purified by preparative HPLC. (Gilson semi preparative HPLC system and a YMC Combiprep Pro Column (50X20mm I.D., C18, S-5 um, 120A) (available from Waters) eluting with 5 - 95% acetonitrile/water (0.1% TFA) at 15 ml/min) to afford the title compound after lyophilization.
- ¹H NMR (d₆DMSO, 400MHz) δ 9.15 (1H, m), 8.91 (0.5H, s), 8.87 (0.5H, s), 8.62-8.50 (1H, m), 7.86-7.75 (1H, m), 4.37 (0.5H, dd, J=10.5 and 7.4Hz), 4.13 (0.5H, m), 4.05-3.40 (4H, m), 2.32 (1H, m) and 2.07 (1H, m) ppm.
- FAB MS calcd for C₁₉H₁₇N₃O₂ 320 (MH⁺), found 320.

EXAMPLE 2

7-[(3-benzylpiperidin-1-yl)carbonyl]-1,6-naphthyridin-8-ol



The title compound was prepared using the procedure described in Example 1, Step 4 replacing 2-phenylpyrrolidine with 3-benzylpiperidine.

¹H NMR (d₆DMSO, 400MHz) δ 9.14 (1H, m), 8.89 (0.5H, s), 8.73 (0.5H, s), 8.58 (1H, m), 7.76 (1H, dd, J=8.3 and 4.3Hz), 7.40-7.10 (3H, m), 7.05-6.60 (2H, m), 4.40 (1H, brd, J=10.3Hz), 4.30 (1H, d, J=11.5Hz) and 3.50-1.00 (9H, m) ppm.
FAB MS calcd for C₂₁H₂₁N₃O₂ 348 (MH⁺), found 348.

EXAMPLE 3

10 Oral Composition

As a specific embodiment of an oral composition of a compound of this invention, 50 mg of compound of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

15

EXAMPLE 4

HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase

Assays for the strand transfer activity of integrase were conducted in accordance with Wolfe, A.L. et al., *J. Virol.* 1996, 70: 1424-1432, for recombinant integrase, except that: (i) the assays used preassembled integrase strand transfer complexes; (ii) the strand transfer reaction was performed in the presence of inhibitor in 2.5 mM MgCl₂ using 0.5 to 5 nM of a 3' FITC labeled target DNA substrate (SEQ. ID. NO.: 1)

25

5'	TGA CCA AGG GCT AAT TCA CT	fitc	3'
3' fitc	ACT GGT TCC CGA TTA AGT GA		5'

and (iii) strand transfer products were detected using an alkaline phosphatase conjugated anti-FITC antibody and a chemiluminescent alkaline phosphatase

substrate. Representative compounds tested in the integrase assay demonstrated IC₅₀'s of less than about 100 micromolar.

Further description on conducting the assay using preassembled complexes is found in Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al.,
5 *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

EXAMPLE 5

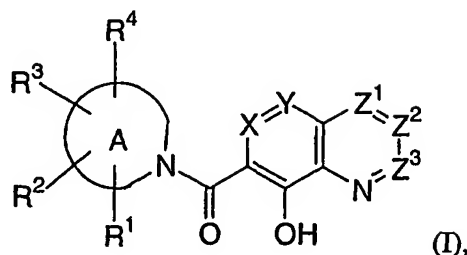
Assay for inhibition of HIV replication

10 Assays for the inhibition of acute HIV infection of T-lymphoid cells were conducted in accordance with Vacca, J.P. et al., (1994), *Proc. Natl. Acad. Sci. USA* 91, 4096. Representative compounds tested in the present assay demonstrated IC₉₅'s of less than about 20 micromolar.

15 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



- 5 wherein A is a 5- or 6-membered saturated or unsaturated heterocyclic ring which contains from 1 to 4 nitrogen atoms one of which is directly attached to the exocyclic carbonyl moiety, zero to 2 heteroatoms selected from oxygen and sulfur, and a balance of carbon atoms; wherein the heterocyclic ring is optionally fused to a phenyl ring or to a second 5- or 6-membered heterocyclic ring which is saturated or
 10 unsaturated and which contains from 1 to 4 nitrogen atoms, zero to 2 heteroatoms selected from oxygen and sulfur, and a balance of carbon atoms, wherein the second heterocyclic ring is optionally fused to a phenyl ring;

A is substituted by R¹, R², R³, and R⁴;

15

X is N or C-Q¹;

Y is N or C-Q², provided that X and Y are not both N;

20 Z¹ is N or C-Q³;

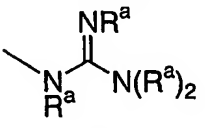
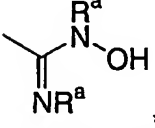
Z² is N or C-Q⁴;

Z³ is N or CH;

25

each of Q¹, Q², Q³, and Q⁴ is independently

- (1) -H,
- (2) -C₁₋₆ alkyl,

- 5
- (3) -C₁₋₆ haloalkyl,
 (4) -O-C₁₋₆ alkyl,
 (5) -O-C₁₋₆ haloalkyl,
 (6) halo,
 (7) -CN,
 (8) -C₁₋₆ alkyl-OR^a,
 (9) -C₀₋₆ alkyl-C(=O)R^a,
 (10) -C₀₋₆ alkyl-CO₂R^a,
 (11) -C₀₋₆ alkyl-SR^a,
 10 (12) -N(R^a)₂,
 (13) -C₁₋₆ alkyl-N(R^a)₂,
 (14) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (15) -C₀₋₆ alkyl-G-C₁₋₆ alkyl-C(=O)N(R^a)₂, wherein G is O, S,
 N(R^a), or N(SO₂R^a),
 15 (16) -N(R^a)-C(R^a)=O,
 (17) -C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (18) -C(=O)-N(R^a)-C₁₋₆ alkyl-[C(=O)]₀₋₁-N(R^a)₂,
 (19) -C(=O)-N(R^a)-C₁₋₆ alkyl substituted with 1 or 2 -OR^a,
 (20) -C₀₋₆ alkyl-SO₂R^a,
 20 (21) -C₀₋₆ alkyl-N(R^a)SO₂R^a,
 (22) -C₂₋₆ alkenyl,
 (23) -C₂₋₆ alkenyl-C(=O)-N(R^a)₂,
 (24) -C₂₋₅ alkynyl,
 (25) -C₂₋₅ alkynyl-CH₂N(R^a)₂,
 25 (26) -C₂₋₅ alkynyl-CH₂OR^a,
 (27) -C₂₋₅ alkynyl-CH₂S(O)_n-R^a, or
- (28) ,
- (29) ,
- 30 (30) -C(=NR^a)-N(R^a)₂,
 (31) -N(R^a)-C₁₋₆ alkyl-S(O)_nR^a,

- 5
- (32) -N(R^a)-C₁₋₆ alkyl-OR^a,
 (33) -N(R^a)-C₁₋₆ alkyl-N(R^a)₂,
 (34) -N(R^a)-C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (35) -N(R^a)-C₀₋₆ alkyl-[C(=O)]₁₋₂N(R^a)₂,
 (36) -N(R^a)-C₁₋₆ alkyl-CO₂R^a,
 (37) -N(R^a)C(=O)N(R^a)-C₁₋₆ alkyl-C(=O)N(R^a)₂,
 (38) -N(R^a)C(=O)-C₁₋₆ alkyl-N(R^a)₂,
 (39) -N(R^a)-SO₂-N(R^a)₂,
 (40) -R^k,
 10 (41) -C₁₋₆ alkyl substituted with R^k,
 (42) -C₁₋₆ haloalkyl substituted with R^k,
 (43) -C₂₋₅ alkenyl-R^k,
 (44) -C₂₋₅ alkynyl-R^k,
 (45) -C₀₋₆ alkyl-O-R^k,
 15 (46) -C₀₋₆ alkyl-O-C₁₋₆ alkyl-R^k,
 (47) -C₀₋₆ alkyl-S(O)_n-R^k,
 (48) -C₀₋₆ alkyl-S(O)_n-C₁₋₆ alkyl-R^k,
 (49) -O-C₁₋₆ alkyl-OR^k,
 (50) -O-C₁₋₆ alkyl-O-C₁₋₆ alkyl-R^k,
 20 (51) -O-C₁₋₆ alkyl-S(O)_nR^k,
 (52) -C₀₋₆ alkyl-N(R^c)-R^k,
 (53) -C₀₋₆ alkyl-N(R^c)-C₁₋₆ alkyl substituted with one or two R^k
 groups,
 (54) -C₀₋₆ alkyl-N(R^c)-C₁₋₆ alkyl-OR^k,
 25 (55) -C₀₋₆ alkyl-C(=O)-R^k,
 (56) -C₀₋₆ alkyl-C(=O)N(R^a)-R^k,
 (57) -C₀₋₆ alkyl-N(R^a)C(=O)-R^k,
 (58) -C₀₋₆ alkyl-C(=O)N(R^a)-C₁₋₆ alkyl-R^k, or
 (59) -C₀₋₆ alkyl-N(R^a)-C₀₋₆ alkyl-S(O)_nR^k;

30

each of R¹ and R² is independently:

- (1) -H,
 (2) -C₁₋₆ alkyl,
 (3) -C₁₋₆ haloalkyl,

- 5
- (4) -O-C₁₋₆ alkyl,
 (5) -O-C₁₋₆ haloalkyl,
 (6) -OH
 (7) halo,
 (8) -NO₂,
 (9) -CN,
 (10) -C₁₋₆ alkyl-OR^a,
 (11) -C₀₋₆ alkyl-C(=O)R^a,
 (12) -C₀₋₆ alkyl-CO₂R^a,
 10 (13) -C₀₋₆ alkyl-SR^a,
 (14) -N(R^a)₂,
 (15) -C₁₋₆ alkyl-N(R^a)₂,
 (16) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (17) -C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 15 (18) -SO₂R^a,
 (19) -N(R^a)SO₂R^a,
 (20) -C₂₋₅ alkenyl,
 (21) -O-C₁₋₆ alkyl-OR^a,
 (22) -O-C₁₋₆ alkyl-SR^a,
 20 (23) -O-C₁₋₆ alkyl-NH-CO₂R^a,
 (24) -O-C₂₋₆ alkyl-N(R^a)₂,
 (25) -N(R^a)-C₁₋₆ alkyl-SR^a,
 (26) -N(R^a)-C₁₋₆ alkyl-OR^a,
 (27) -N(R^a)-C₁₋₆ alkyl-N(R^a)₂,
 25 (28) -N(R^a)-C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (29) -R^k,
 (30) -C₁₋₆ alkyl substituted with 1 or 2 R^k groups,
 (31) -C₁₋₆ haloalkyl substituted with 1 or 2 R^k groups,
 (32) -C₂₋₅ alkenyl-R^k,
 30 (33) -C₂₋₅ alkynyl-R^k,
 (34) -O-R^k,
 (35) -O-C₁₋₆ alkyl-R^k,
 (36) -S(O)_n-R^k,
 (37) -S(O)_n-C₁₋₆ alkyl-R^k,

- (38) -O-C₁₋₆ alkyl-OR^k,
 (39) -O-C₁₋₆ alkyl-O-C₁₋₆ alkyl-R^k,
 (40) -O-C₁₋₆ alkyl-S(O)_nR^k,
 (41) -C₁₋₆ alkyl (OR^b)(R^k) ,
 5 (42) -C₁₋₆ alkyl (OR^b)(-C₁₋₆ alkyl-R^k) ,
 (43) -C₀₋₆ alkyl-N(R^b)(R^k),
 (44) -C₀₋₆ alkyl-N(R^b)(-C₁₋₆ alkyl-R^k),
 (45) -C₁₋₆ alkyl S(O)_n-R^k,
 (46) -C₁₋₆ alkyl S(O)_n-C₁₋₆ alkyl-R^k,
 10 (47) -C₀₋₆ alkyl C(O)-R^k, or
 (48) -C₀₋₆ alkyl C(O)-C₁₋₆ alkyl-R^k,

each of R³ and R⁴ is independently

- (1) -H,
 15 (2) halo,
 (3) -CN,
 (4) -NO₂,
 (5) -OH,
 (6) C₁₋₆ alkyl,
 20 (7) C₁₋₆ haloalkyl,
 (8) -O-C₁₋₆ alkyl,
 (9) -O-C₁₋₆ haloalkyl,
 (10) -C₁₋₆ alkyl-OR^a,
 (11) -C₀₋₆ alkyl-C(=O)R^a,
 25 (12) -C₀₋₆ alkyl-CO₂R^a,
 (13) -C₀₋₆ alkyl-SR^a,
 (14) -N(R^a)₂,
 (15) -C₁₋₆ alkyl-N(R^a)₂,
 (16) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 30 (17) -SO₂R^a,
 (18) -N(R^a)SO₂R^a,
 (19) -C₂₋₅ alkenyl,
 (20) -O-C₁₋₆ alkyl-OR^a,
 (21) -O-C₁₋₆ alkyl-SR^a,

(22) -O-C₁₋₆ alkyl-NH-CO₂R^a,

(23) -O-C₂₋₆ alkyl-N(R^a)₂, or

(24) oxo;

5 each R^a is independently -H, -C₁₋₆ alkyl, or -C₁₋₆ haloalkyl;

each R^b is independently:

- (1) -H,
- (2) -C₁₋₄ alkyl,
- 10 (3) -C₁₋₄ haloalkyl,
- (4) -R^k,
- (5) -C₂₋₃ alkenyl,
- (6) -C₁₋₄ alkyl-R^k,
- (7) -C₂₋₃ alkenyl-R^k,
- 15 (8) -S(O)_n-R^k, or
- (9) -C(O)-R^k;

each R^c is independently

- (1) -H,
- 20 (2) -C₁₋₆ alkyl,
- (3) -C₁₋₆ alkyl substituted with -N(R^a)₂, or
- (4) -C₁₋₄ alkyl-aryl, wherein aryl is optionally substituted with 1 to 5 substituents independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, -O-C₁₋₆ haloalkyl, -S-C₁₋₆
- 25 alkyl, -CN, and -OH;

each R^k is independently carbocycle or heterocycle, wherein the carbocycle and heterocycle are unsubstituted or substituted with from 1 to 5 substituents each of which is independently selected from

- 30 (a) halogen,
- (b) -C₁₋₆ alkyl,
- (c) -C₁₋₆ haloalkyl,
- (d) -O-C₁₋₆ alkyl,
- (e) -O-C₁₋₆ haloalkyl,

- 5 (f) -S-C₁₋₆ alkyl,
 (g) -CN,
 (h) -OH,
 (i) oxo,
 (j) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (k) -C₀₋₆ alkyl-C(=O)R^a,
 (l) -N(R^a)-C(=O)R^a,
 (m) -N(R^a)-CO₂R^a,
 (n) -C₁₋₆ alkyl-N(R^a)-C(=O)R^a,
 10 (o) -N(R^a)₂,
 (p) -C₁₋₆ alkyl-N(R^a)₂,
 (q) -C₁₋₆ alkyl-OR^a,
 (r) -C₀₋₆ alkyl-CO₂R^a,
 (s) -C₀₋₆ alkyl-O-C₁₋₆ alkyl-OR^a,
 15 (t) -SO₂R^a,
 (u) -SO₂N(R^a)₂,
 (v) -C₀₋₆ alkyl-CO₂-C₂₋₅ alkenyl,
 (w) aryl,
 (x) aryloxy-,
 20 (y) -C₁₋₄ alkyl substituted with aryl,
 (z) heteromonocycle,
 (aa) -C₁₋₄ alkyl substituted with a heteromonocycle,
 (bb) heteromonocyclylcarbonyl-C₀₋₆ alkyl-, and
 (cc) N-heteromonocyclyl-N-C₁₋₆ alkyl-amino-;
 25 wherein the aryl group in (w) aryl, (x) aryloxy, and (y) -C₁₋₄
 alkyl substituted with aryl, is optionally substituted with from 1 to 4
 substituents independently selected from halogen, C₁₋₆ alkyl, -O-C₁₋₆
 alkyl, C₁₋₆ alkyl substituted with N(R^a)₂, C₁₋₆ haloalkyl, and -OH;
 and
 30 wherein the heteromonocyclyl group in (z) heteromonocycle,
 (aa) -C₁₋₄ alkyl substituted with a heteromonocycle,
 (bb) heteromonocyclyl-carbonyl-C₀₋₆ alkyl-, and (cc) N-
 heteromonocyclyl-N-C₁₋₆ alkyl-amino- is optionally substituted with

from 1 to 4 substituents independently selected from halogen, C₁₋₆ alkyl, -O-C₁₋₆ alkyl, C₁₋₆ haloalkyl, oxo, and -OH; and

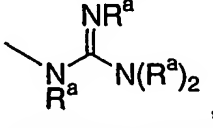
each n is independently an integer equal to 0, 1 or 2;

5

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein:

10 each of Q¹, Q², Q³ and Q⁴ is independently

- (1) -H,
- (2) -C₁₋₆ alkyl,
- (3) -C₁₋₆ fluoroalkyl,
- (4) -O-C₁₋₆ alkyl,
- 15 (5) -O-C₁₋₆ fluoroalkyl,
- (6) halo,
- (7) -CN,
- (8) -C₁₋₆ alkyl-OR^a,
- (9) -C₀₋₆ alkyl-C(=O)R^a,
- 20 (10) -C₀₋₆ alkyl-CO₂R^a,
- (11) -C₀₋₆ alkyl-SR^a,
- (12) -N(R^a)₂,
- (13) -C₁₋₆ alkyl -N(R^a)₂,
- (14) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
- 25 (15) -C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
- (16) -SO₂R^a,
- (17) -N(R^a)SO₂R^a,
- (18) -C₂₋₅ alkynyl,
- (19) -C₂₋₅ alkynyl-CH₂N(R^a)₂,
- 30 (20) -C₂₋₅ alkynyl-CH₂OR^a,
- (21) ,
CN(R^a)C(=NR^a)N(R^a)_2
- (22) -N(R^a)-C₁₋₆ alkyl-SR^a,

- (23) -N(R^a)-C₁₋₆ alkyl-OR^a,
 (24) -N(R^a)-C₁₋₆ alkyl-N(R^a)₂,
 (25) -N(R^a)-C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (26) -R^k,
 5 (27) -C₁₋₆ alkyl substituted with R^k,
 (28) -C₁₋₆ fluoroalkyl substituted with R^k,
 (29) -C₂₋₅ alkenyl-R^k,
 (30) -C₂₋₅ alkynyl-R^k,
 (31) -O-R^k,
 10 (32) -O-C₁₋₄ alkyl-R^k,
 (33) -S(O)_n-R^k,
 (34) -S(O)_n-C₁₋₄ alkyl-R^k,
 (35) -O-C₁₋₆ alkyl-OR^k,
 (36) -O-C₁₋₆ alkyl-O-C₁₋₄ alkyl-R^k,
 15 (37) -O-C₁₋₆ alkyl-SR^k,
 (38) -N(R^c)-R^k,
 (39) -N(R^c)-C₁₋₆ alkyl substituted with one or two R^k groups,
 (40) -N(R^c)-C₁₋₆ alkyl-OR^k,
 (41) -C(=O)N-C₁₋₆ alkyl-R^k,
 20 (42) -C₂₋₅ alkynyl-CH₂S(O)_n-R^a, or
 (43) -C(=NR^a)-N(R^a)₂;

each of R¹ and R² is independently:

- (1) -H,
 25 (2) -C₁₋₆ alkyl,
 (3) -C₁₋₆ fluoroalkyl,
 (4) -O-C₁₋₆ alkyl,
 (5) -O-C₁₋₆ fluoroalkyl,
 (6) -OH,
 30 (7) halo,
 (8) -NO₂,
 (9) -CN,
 (10) -C₁₋₆ alkyl-OR^a,
 (11) -C₀₋₆ alkyl-C(=O)R^a,

- (12) -C₀₋₆ alkylCO₂R^a,
 (13) -C₀₋₆ alkyl-SR^a,
 (14) -N(R^a)₂,
 (15) -C₁₋₆ alkyl N(R^a)₂,
 5 (16) -C₀₋₆ alkyl-C(=O)N(R^a)₂,
 (17) -C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (18) -SO₂R^a,
 (19) -N(R^a)SO₂R^a,
 (20) -C₂₋₅ alkenyl,
 10 (21) -O-C₁₋₆ alkyl-OR^a,
 (22) -O-C₁₋₆ alkyl-SR^a,
 (23) -O-C₁₋₆ alkyl-NH-CO₂R^a,
 (24) -O-C₂₋₆ alkyl-N(R^a)₂,
 (25) -N(R^a)-C₁₋₆ alkyl-SR^a,
 15 (26) -N(R^a)-C₁₋₆ alkyl-OR^a,
 (27) -N(R^a)-C₁₋₆ alkyl-N(R^a)₂,
 (28) -N(R^a)-C₁₋₆ alkyl-N(R^a)-C(R^a)=O,
 (29) -R^k,
 (30) -C₁₋₆ alkyl substituted with 1 or 2 R^k groups,
 20 (31) -C₁₋₆ fluoroalkyl substituted with 1 or 2 R^k groups,
 (32) -C₂₋₅ alkenyl-R^k,
 (33) -C₂₋₅ alkynyl-R^k,
 (34) -O-R^k,
 (35) -O-C₁₋₄ alkyl-R^k,
 25 (36) -S(O)_n-R^k,
 (37) -S(O)_n-C₁₋₄ alkyl-R^k,
 (38) -O-C₁₋₆ alkyl-OR^k,
 (39) -O-C₁₋₆ alkyl-O-C₁₋₄ alkyl-R^k,
 (40) -O-C₁₋₆ alkyl-SR^k,
 30 (41) -C₁₋₆ alkyl (OR^b)(R^k) ,
 (42) -C₁₋₆ alkyl (OR^b)(-C₁₋₄ alkyl-R^k) ,
 (43) -C₀₋₆ alkyl-N(R^b)(R^k),
 (44) -C₀₋₆ alkyl-N(R^b)(-C₁₋₄ alkyl-R^k),
 (45) -C₁₋₆ alkyl S(O)_n-R^k,

- (46) $-C_{1-6}$ alkyl $S(O)_n-C_{1-4}$ alkyl- R^k ,
 (47) $-C_{0-6}$ alkyl $C(O)-R^k$, or
 (48) $-C_{0-6}$ alkyl $C(O)-C_{1-4}$ alkyl- R^k ,

5 each of R^3 and R^4 is independently

- (1) $-H$,
 (2) halo,
 (3) $-CN$,
 (4) $-NO_2$,
 10 (5) $-OH$,
 (6) C_{1-6} alkyl,
 (7) C_{1-6} fluoroalkyl,
 (8) $-O-C_{1-6}$ alkyl,
 (9) $-O-C_{1-6}$ fluoroalkyl,
 15 (10) $-C_{1-6}$ alkyl- OR^a ,
 (11) $-C_{0-6}$ alkyl- $C(=O)R^a$,
 (12) $-C_{0-6}$ alkyl- CO_2R^a ,
 (13) $-C_{0-6}$ alkyl- SR^a ,
 (14) $-N(R^a)_2$,
 20 (15) $-C_{1-6}$ alkyl $N(R^a)_2$,
 (16) $-C_{0-6}$ alkyl- $C(=O)N(R^a)_2$,
 (17) $-SO_2R^a$,
 (18) $-N(R^a)SO_2R^a$,
 (19) $-C_{2-5}$ alkenyl,
 25 (20) $-O-C_{1-6}$ alkyl- OR^a ,
 (21) $-O-C_{1-6}$ alkyl- SR^a ,
 (22) $-O-C_{1-6}$ alkyl- $NH-CO_2R^a$,
 (23) $-O-C_{2-6}$ alkyl- $N(R^a)_2$, or
 (24) oxo

30

each R^a is independently $-H$, $-C_{1-6}$ alkyl, or $-C_{1-6}$ fluoroalkyl;

each R^b is independently:

- (1) $-H$,

- 5
- (2) -C₁₋₄ alkyl,
 - (3) -C₁₋₄ fluoroalkyl,
 - (4) -R^k,
 - (5) -C₂₋₃ alkenyl,
 - (6) -C₁₋₄ alkyl-R^k,
 - (7) -C₂₋₃ alkenyl-R^k,
 - (8) -S(O)_n-R^k, or
 - (9) -C(O)-R^k;

10 each R^c is independently

- 15
- (1) -H,
 - (2) -C₁₋₆ alkyl,
 - (3) -C₁₋₆ alkyl substituted with -N(R^a)₂, or
 - (4) -C₁₋₄ alkyl-aryl, wherein aryl is optionally substituted with 1 to 5 substituents independently selected from halogen, C₁₋₆ alkyl, C₁₋₆ fluoroalkyl, -O-C₁₋₆ alkyl, -O-C₁₋₆ fluoroalkyl, -S-C₁₋₆ alkyl, -CN, and -OH;

20 each R^k is independently carbocycle or heterocycle, wherein the carbocycle and heterocycle are unsubstituted or substituted with from 1 to 5 substituents each of which is independently selected from

- 25
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ fluoroalkyl,
 - (d) -O-C₁₋₆ alkyl,
 - (e) -O-C₁₋₆ fluoroalkyl,
 - (f) -S-C₁₋₆ alkyl,
 - (g) -CN,
 - (h) -OH,
 - 30 (i) oxo,
 - (j) -(CH₂)₀₋₃C(=O)N(R^a)₂,
 - (k) -(CH₂)₀₋₃C(=O)R^a,
 - (l) -N(R^a)-C(=O)R^a,
 - (m) -N(R^a)-C(=O)OR^a,

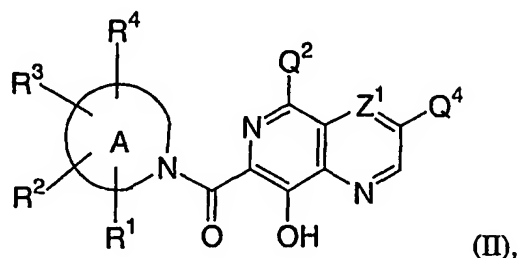
- (n) $-(\text{CH}_2)_{1-3}\text{N}(\text{R}^a)\text{-C(=O)R}^a$,
 (o) $-\text{N}(\text{R}^a)_2$,
 (p) $-\text{C}_{1-6}\text{ alkyl-N}(\text{R}^a)_2$,
 (q) aryl,
 (r) aryloxy-,
 (s) $-\text{C}_{1-4}\text{ alkyl}$ substituted with aryl,
 (t) heteromonocycle,
 (u) $-\text{C}_{1-4}\text{ alkyl}$ substituted with a heteromonocycle,
 (v) heteromonocyclylcarbonyl- $\text{C}_{0-6}\text{ alkyl-}$, and
 (w) N-heteromonocyclyl-N- $\text{C}_{1-6}\text{ alkyl-amino-}$;

wherein the aryl group in (q) aryl, (r) aryloxy, and (s) $-\text{C}_{1-4}\text{ alkyl}$ substituted with aryl, is optionally substituted with from 1 to 3 substituents independently selected from halogen, $\text{C}_{1-6}\text{ alkyl}$, $-\text{O-C}_{1-6}\text{ alkyl}$, $\text{C}_{1-6}\text{ alkyl}$ substituted with $\text{N}(\text{R}^a)_2$, $\text{C}_{1-6}\text{ fluoroalkyl}$, and $-\text{OH}$;
 and

wherein the heteromonocyclyl group in (t) heteromonocycle, (u) $-\text{C}_{1-4}\text{ alkyl}$ substituted with a heteromonocycle, (v) heteromonocyclyl-carbonyl- $\text{C}_{0-6}\text{ alkyl-}$, and (w) N-heteromonocyclyl-N- $\text{C}_{1-6}\text{ alkyl-amino-}$ is optionally substituted with from 1 to 3 substituents independently selected from halogen, $\text{C}_{1-6}\text{ alkyl}$, $-\text{O-C}_{1-6}\text{ alkyl}$, $\text{C}_{1-6}\text{ fluoroalkyl}$, oxo, and $-\text{OH}$;

or a pharmaceutically acceptable salt thereof.

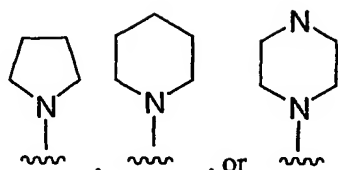
3. The compound according to claim 2, which is a compound of Formula (II):



wherein

A is

5



, or ; where “~” denotes the point of attachment;

Z¹ is N or C-Q³;

10 Q² is

- (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -C₁₋₄ fluoroalkyl,
- (4) -O-C₁₋₄ alkyl,
- 15 (5) -O-C₁₋₄ fluoroalkyl,
- (6) halo,
- (7) -CN,
- (8) -C₁₋₄ alkyl-OR^a,
- (9) -(CH₂)₀₋₂C(=O)R^a,
- 20 (10) -(CH₂)₀₋₂CO₂R^a,
- (11) -(CH₂)₀₋₂SR^a,
- (12) -N(R^a)₂,
- (13) -C₁₋₄ alkyl -N(R^a)₂,
- (14) -(CH₂)₀₋₂C(=O)N(R^a)₂,
- 25 (15) -SO₂R^a,
- (16) -N(R^a)SO₂R^a,
- (17) -C₂₋₃ alkynyl,
- (18) —C≡C—CH₂N(R^a)₂ ,
- (19) —C≡C—CH₂OR^a ,
- 30 (20) -N(R^a)-C₁₋₄ alkyl-SR^a,

- (21) $-N(R^a)-C_{1-4} \text{ alkyl}-OR^a$,
 (22) $-N(R^a)-C_{1-4} \text{ alkyl}-N(R^a)_2$,
 (23) $-N(R^a)-C_{1-4} \text{ alkyl}-N(R^a)-C(R^a)=O$,
 (24) $-R^k$,
 5 (25) $-C_{1-4} \text{ alkyl}$ substituted with R^k ,
 (26) $-C_{1-4} \text{ fluoroalkyl}$ substituted with R^k ,
 (27) $-C_{2-5} \text{ alkenyl}-R^k$,
 (28) $-C_{2-5} \text{ alkynyl}-R^k$,
 (29) $-O-R^k$,
 10 (30) $-O-C_{1-4} \text{ alkyl}-R^k$,
 (31) $-S(O)_n-R^k$,
 (32) $-N(R^c)-R^k$,
 (33) $-N(R^c)-C_{1-4} \text{ alkyl}$ substituted with one or two R^k groups,
 (34) $-N(R^c)-C_{1-4} \text{ alkyl}-OR^k$,
 15 (35) $-C(=O)N-C_{1-4} \text{ alkyl}-R^k$,
 (36) $-C\equiv C-CH_2SR^a$, or
 (37) $-C\equiv C-CH_2SO_2R^a$;

Q^3 is

- 20 (1) $-H$,
 (2) $-C_{1-4} \text{ alkyl}$,
 (3) $-C_{1-4} \text{ fluoroalkyl}$,
 (4) $-O-C_{1-4} \text{ alkyl}$,
 (5) $-O-C_{1-4} \text{ fluoroalkyl}$,
 25 (6) halo selected from $-F$, $-Cl$, and $-Br$,
 (7) $-CN$,
 (8) $-C_{1-4} \text{ alkyl}-OR^a$, or
 (9) $-C_{1-4} \text{ alkyl}$ substituted with R^k ;

30 Q^4 is:

- (1) $-H$,
 (2) $-C_{1-4} \text{ alkyl}$,
 (3) $-C_{1-4} \text{ fluoroalkyl}$,
 (4) $-O-C_{1-4} \text{ alkyl}$,

- 5
- (5) -O-C₁₋₄ fluoroalkyl,
 - (6) halo selected from -F, -Cl, and -Br,
 - (7) -CN,
 - (8) -C₁₋₆ alkyl-OR^a,
 - (9) -N(R^a)₂, or
 - (10) -C₁₋₆ alkyl -N(R^a)₂;

each of R¹ and R² is independently:

- 10
- (1) -H,
 - (2) -C₁₋₄ alkyl,
 - (3) -C₁₋₄ fluoroalkyl,
 - (4) -O-C₁₋₄ alkyl,
 - (5) -O-C₁₋₄ fluoroalkyl,
 - (6) -OH,
 - 15 (7) halo,
 - (8) -CN,
 - (9) -C₁₋₄ alkyl-OR^a,
 - (10) -(CH₂)₀₋₂C(=O)R^a,
 - (11) -(CH₂)₀₋₂CO₂R^a,
 - 20 (12) -(CH₂)₀₋₂SR^a,
 - (13) -N(R^a)₂,
 - (14) -C₁₋₄ alkyl N(R^a)₂,
 - (15) -(CH₂)₀₋₂C(=O)N(R^a)₂,
 - (16) -C₁₋₄ alkyl-N(R^a)-C(R^a)=O,
 - 25 (17) -SO₂R^a,
 - (18) -N(R^a)SO₂R^a,
 - (19) -O-C₁₋₄ alkyl-OR^a,
 - (20) -O-C₁₋₄ alkyl-SR^a,
 - (21) -O-C₁₋₄ alkyl-NH-CO₂R^a,
 - 30 (22) -O-C₂₋₄ alkyl-N(R^a)₂,
 - (23) -N(R^a)-C₁₋₄ alkyl-SR^a,
 - (24) -N(R^a)-C₁₋₄ alkyl-OR^a,
 - (25) -N(R^a)-C₁₋₄ alkyl-N(R^a)₂,
 - (26) -N(R^a)-C₁₋₄ alkyl-N(R^a)-C(R^a)=O,

- (27) $-R^k$,
 (28) $-C_{1-4}$ alkyl substituted with 1 or 2 R^k groups,
 (29) $-C_{1-4}$ fluoroalkyl substituted with 1 or 2 R^k groups,
 (30) $-O-R^k$,
 5 (31) $-O-C_{1-4}$ alkyl- R^k ,
 (32) $-S(O)_n-R^k$,
 (33) $-S(O)_n-C_{1-4}$ alkyl- R^k ,
 (34) $-O-C_{1-4}$ alkyl- OR^k ,
 (35) $-O-C_{1-4}$ alkyl- $O-C_{1-4}$ alkyl- R^k ,
 10 (36) $-O-C_{1-4}$ alkyl- SR^k , or
 (37) $-C_{0-4}$ alkyl- $N(R^b)(R^k)$;

each of R^3 and R^4 is independently

- (1) $-H$,
 15 (2) halo,
 (3) $-CN$,
 (4) $-OH$,
 (5) C_{1-4} alkyl,
 (6) C_{1-4} fluoroalkyl,
 20 (7) $-O-C_{1-4}$ alkyl,
 (8) $-O-C_{1-4}$ fluoroalkyl,
 (9) $-C_{1-4}$ alkyl- OR^a ,
 (10) $-O-C_{1-4}$ alkyl- OR^a ,
 (11) $-O-C_{1-4}$ alkyl- SR^a ,
 25 (12) $-O-C_{1-4}$ alkyl- $NH-CO_2R^a$, or
 (13) $-O-C_{2-4}$ alkyl- $N(R^a)_2$;

each R^a is independently $-H$ or $-C_{1-4}$ alkyl;

30 each R^b is independently:

- (1) $-H$,
 (2) $-C_{1-4}$ alkyl,
 (3) $-C_{1-4}$ fluoroalkyl,
 (4) $-R^k$,

- (5) $-C_{1-4}$ alkyl- R^k ,
- (6) $-S(O)_n-R^k$, or
- (7) $-C(=O)-R^k$;

5 each R^c is independently

- (1) $-H$,
 - (2) $-C_{1-4}$ alkyl,
 - (3) $-C_{1-4}$ alkyl substituted with $-N(R^a)_2$, or
 - (4) $-C_{1-4}$ alkyl-phenyl, wherein the phenyl is optionally substituted
- 10 with 1 to 3 substituents independently selected from halogen, C_{1-4} alkyl, C_{1-4} fluoroalkyl, $-O-C_{1-4}$ alkyl, $-O-C_{1-4}$ fluoroalkyl, $-S-C_{1-4}$ alkyl, $-CN$, and $-OH$;

each R^k is independently:

- 15 (1) aryl selected from phenyl and naphthyl, wherein aryl is unsubstituted or substituted with from 1 to 5 substituents independently selected from:
- (a) halogen,
 - (b) C_{1-6} alkyl,
 - (c) C_{1-6} fluoroalkyl,
 - 20 (d) $-O-C_{1-6}$ alkyl,
 - (e) $-O-C_{1-6}$ fluoroalkyl,
 - (f) phenyl,
 - (g) $-S-C_{1-6}$ alkyl,
 - (h) $-CN$,
 - 25 (i) $-OH$,
 - (j) phenoxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
 - (i) halogen,
 - (ii) C_{1-6} alkyl,
 - 30 (iii) C_{1-6} fluoroalkyl, and
 - (iv) $-OH$,
 - (k) $-N(R^a)_2$,
 - (l) $-C_{1-6}$ alkyl- $N(R^a)_2$,
 - (m) $-R^t$,

- (p) $-(\text{CH}_2)_{0-3}\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, and
(q) $-(\text{CH}_2)_{0-3}\text{C}(=\text{O})\text{R}^a$;
- (2) $-\text{C}_{3-7}$ cycloalkyl, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
- 5 (a) halogen,
(b) C_{1-6} alkyl,
(c) $-\text{O}-\text{C}_{1-6}$ alkyl,
(d) C_{1-6} fluoroalkyl,
(e) $-\text{O}-\text{C}_{1-6}$ fluoroalkyl,
- 10 (f) $-\text{CN}$,
(h) phenyl, and
(j) $-\text{OH}$;
- (3) $-\text{C}_{3-7}$ cycloalkyl fused with a phenyl ring, unsubstituted or substituted with from 1 to 5 substituents independently selected from:
- 15 (a) halogen,
(b) C_{1-6} alkyl,
(c) $-\text{O}-\text{C}_{1-6}$ alkyl,
(d) C_{1-6} fluoroalkyl,
(e) $-\text{O}-\text{C}_{1-6}$ fluoroalkyl,
- 20 (f) $-\text{CN}$, and
(g) $-\text{OH}$;
- (4) a 5- or 6- membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heteroaromatic ring is unsubstituted or substituted on nitrogen or carbon with from 1
- 25 to 5 substituents independently selected from:
- (a) halogen,
(b) C_{1-6} alkyl,
(c) C_{1-6} fluoroalkyl,
(d) $-\text{O}-\text{C}_{1-6}$ alkyl,
- 30 (e) $-\text{O}-\text{C}_{1-6}$ fluoroalkyl,
(f) phenyl,
(g) $-\text{S}-\text{C}_{1-6}$ alkyl,
(h) $-\text{CN}$,
(i) $-\text{OH}$,

- (j) phenyloxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
- (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) C₁₋₆ fluoroalkyl, and
 - (iv) -OH,
- (k) -N(R^a)₂,
- (l) -C₁₋₆ alkyl-N(R^a)₂,
- (m) -R^t,
- (n) oxo,
- (o) -(CH₂)₀₋₃C(=O)N(R^a)₂, and
- (p) -(CH₂)₀₋₃C(=O)R^a;
- (5) a 5- or 6- membered saturated heterocyclic ring containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heterocyclic ring is unsubstituted or substituted with from 1 to 4 substituents independently selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) -O-C₁₋₆ alkyl,
 - (d) C₁₋₆ fluoroalkyl,
 - (e) -O-C₁₋₆ fluoroalkyl,
 - (f) -CN,
 - (g) oxo,
 - (h) phenyl,
 - (i) benzyl,
 - (j) phenylethyl,
 - (k) -OH,
 - (l) -(CH₂)₀₋₃C(=O)N(R^a)₂,
 - (m) -(CH₂)₀₋₃C(=O)R^a,
 - (n) -N(R^a)-C(=O)R^a,
 - (o) -N(R^a)-C(=O)OR^a,
 - (p) -(CH₂)₁₋₃N(R^a)-C(=O)R^a,
 - (q) -N(R^a)₂,
 - (r) -(CH₂)₁₋₃N(R^a)₂,

- (s) $-(CH_2)_{0-3}C(=O)R^t$,
 - (t) $-R^t$,
 - (u) $-N(R^a)R^t$, and
 - (v) $-(CH_2)_{1-3}R^t$; or
- 5 (6) an 8- to 10- membered heterobicyclic ring containing from 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein the heterobicyclic ring is saturated or unsaturated, and is unsubstituted or substituted with from 1 to 5 substituents independently selected from:
- (a) halogen,
 - 10 (b) C_{1-6} alkyl,
 - (c) $-O-C_{1-6}$ alkyl,
 - (d) C_{1-6} fluoroalkyl,
 - (e) $-O-C_{1-6}$ fluoroalkyl,
 - (f) $-CN$,
 - 15 (g) $=O$, and
 - (h) $-OH$;

R^t is naphthyl or a 5- or 6-membered heteromonocyclic ring containing from 1 to 4 nitrogen atoms, wherein the heteromonocyclic ring is saturated or unsaturated, and
 20 wherein the naphthyl or the heteromonocyclic ring is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, oxo, C_{1-4} alkyl, and $-O-C_{1-4}$ alkyl; and

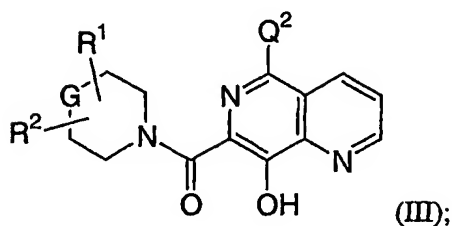
n is an integer equal to 0, 1 or 2;
 25 or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 3, wherein
 30 Z^1 is CH ; and

Q^4 is $-H$;

or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 2, which is a compound of Formula (III):



wherein G is:

- (1) NH optionally substituted by either R¹ or R²,
- (2) CH₂ optionally substituted by either or both R¹ and R², or
- (3) -S(O)_n wherein n is an integer equal to zero, 1 or 2;

Q² is

- (1) -H,
- (2) methyl,
- (3) ethyl,
- (4) CF₃,
- (5) methoxy,
- (6) ethoxy
- (7) -OCF₃
- (8) halo selected from -F, -Cl and -Br,
- (9) -CN,
- (10) -CH₂OH,
- (11) -CH₂OCH₃
- (12) -(CH₂)₀₋₂CO₂CH₃,
- (13) -SR^a,
- (14) -N(R^a)₂,
- (15) -SO₂R^a,
- (16) -C≡C-CH₂OR^a,
- (17) -N(R^a)-(CH₂)₁₋₃SR^a,

- (18) $-N(R^a)-(CH_2)_{1-3}OR^a$,
 (19) $-N(R^a)-(CH_2)_{1-3}N(R^a)_2$,
 (20) $-N(R^a)-(CH_2)_{1-3}N(R^a)-C(R^a)=O$,
 (21) $-R^k$,
 5 (22) $-(CH_2)_{1-4}R^k$,
 (23) $-C\equiv C-CH_2R^k$,
 (24) $-O-R^k$,
 (25) $-S-R^k$,
 (26) $-SO_2-R^k$,
 10 (27) $-N(R^c)-R^k$,
 (28) $-N(R^c)-(CH_2)_{1-4}H$ substituted with one or two R^k groups,
 (29) $-N(R^c)-(CH_2)_{1-4}OR^k$,
 (30) $-C(=O)N-(CH_2)_{1-4}R^k$,
 (31) $-C\equiv C-CH_2SR^a$, or
 15 (32) $-C\equiv C-CH_2SO_2R^a$;

each of R^1 and R^2 is independently:

- (1) $-H$,
 (2) methyl,
 20 (3) ethyl,
 (4) CF_3 ,
 (5) methoxy,
 (6) ethoxy,
 (7) $-OCF_3$,
 25 (8) halo selected from $-F$, $-Cl$ and $-Br$,
 (9) $-CN$,
 (10) $-CH_2OR^a$,
 (11) $-CO_2R^a$,
 (12) $-SR^a$,
 30 (13) $-N(R^a)_2$,
 (14) $-(CH_2)_{1-3}N(R^a)_2$,
 (15) $-SO_2R^a$,
 (16) $-(CH_2)_{1-2}N(R^a)-C(R^a)=O$,
 (17) $-R^k$,

(18) $-(CH_2)_{1-3}H$ substituted with 1 or 2 R^k groups,

(19) $-OR^k$, or

(20) $-O-(CH_2)_{1-3}R^k$;

5 each R^a is independently $-H$ or $-C_{1-4}$ alkyl;

each R^c is independently $-H$, $-C_{1-4}$ alkyl, or $-(CH_2)_{1-3}N(R^a)_2$;

each R^k is independently:

10 (1) phenyl which is unsubstituted or substituted with from 1 to 4 substituents independently selected from:

(a) halogen selected from $-F$, $-Cl$, and $-Br$,

(b) methyl,

(c) $-CF_3$,

15 (d) methoxy,

(e) $-OCF_3$,

(f) phenyl,

(g) $-S-CH_3$,

(h) $-CN$,

20 (i) $-OH$,

(j) phenyloxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:

(i) halogen selected from $-F$, $-Cl$, and $-Br$,

(ii) methyl,

25 (iii) $-CF_3$, and

(iv) $-OH$,

(k) $-N(R^a)_2$,

(l) $-(CH_2)_{1-3}N(R^a)_2$,

(m) $-R^t$,

30 (p) $-(CH_2)_{0-3}C(=O)N(R^a)_2$, and

(q) $-(CH_2)_{0-3}C(=O)R^a$;

(2) $-C_{3-6}$ cycloalkyl, unsubstituted or substituted with from 1 to 3 substituents independently selected from:

(a) halogen selected from $-F$, $-Cl$, and $-Br$,

- 5
- (b) methyl,
 - (c) -CF₃,
 - (d) methoxy,
 - (e) -OCF₃,
 - (f) -CN,
 - (h) phenyl, and
 - (j) -OH;
- (3) a 5- or 6- membered heteroaromatic ring selected from thienyl, pyridyl, imidazolyl, pyrrolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, furanyl, and pyridazinyl, wherein the
- 10 heteroaromatic ring is unsubstituted or substituted on nitrogen or carbon with 1 or 2 substituents independently selected from:
- (a) halogen selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) -CF₃,
 - (d) methoxy,
 - (e) -OCF₃,
 - (f) phenyl,
 - (g) -S-C₁₋₆ alkyl,
 - (h) -CN,
 - (i) -OH,
 - (j) phenyloxy, unsubstituted or substituted with from 1 to 3 substituents independently selected from:
 - (i) halogen selected from -F, -Cl, and -Br,
 - (ii) methyl,
 - (iii) -CF₃, and
 - (iv) -OH,
 - (k) -N(R^a)₂,
 - (l) -C₁₋₆ alkyl-N(R^a)₂,
 - (m) -R^t,
 - (n) oxo,
 - (o) -(CH₂)₀₋₃C(=O)N(R^a)₂, and
 - (p) -(CH₂)₀₋₃C(=O)R^a;
- 15
- 20
- 25
- 30

- (4) a 5- or 6- membered saturated heterocyclic ring selected from piperidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isooxazolidinyl, pyrrolidinyl, imidazolidinyl, piperazinyl, tetrahydrofuranyl, and pyrazolidinyl, wherein the heterocyclic ring is unsubstituted or substituted with 1 or 2 substituents independently selected from:
- (a) halogen selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) -CF₃,
 - (d) methoxy,
 - (e) -OCF₃,
 - (f) -CN,
 - (g) =O,
 - (h) phenyl,
 - (i) benzyl,
 - (j) phenylethyl,
 - (k) -OH,
 - (l) -(CH₂)₀₋₃C(=O)N(R^a)₂,
 - (m) -(CH₂)₀₋₃C(=O)R^a,
 - (n) N(R^a)-C(=O)R^a,
 - (o) N(R^a)-C(=O)OR^a,
 - (p) (CH₂)₁₋₃N(R^a)-C(=O)R^a,
 - (q) N(R^a)₂,
 - (r) (CH₂)₁₋₃N(R^a)₂,
 - (s) -(CH₂)₀₋₃C(=O)R^t,
 - (t) -R^t,
 - (u) -N(R^a)R^t, and
 - (v) -(CH₂)₁₋₃R^t; and

- (5) an 8- to 10- membered heterobicyclic ring selected from indolyl, benzotriazolyl, benzoimidazolyl, imidazo[4,5-b]pyridinyl, dihydroimidazo[4,5-b]pyridinyl, pyrazolo[4,3-c]pyridinyl, dihydropyrazolo[4,3-c]pyridinyl, tetrahydropyrazolo[4,3-c]pyridinyl, pyrrolo[1,2-a]pyrazinyl, dihydropyrrolo[1,2-a]pyrazinyl, tetrahydropyrrolo[1,2-a]pyrazinyl, octahydropyrrolo[1,2-a]pyrazinyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinoxalinyl, cinnolinyl, chromanyl, and

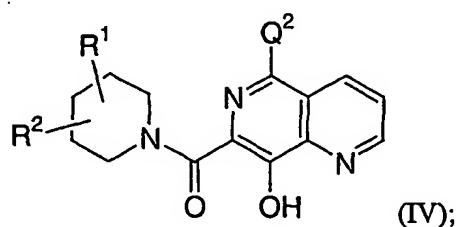
isochromanyl, wherein the bicyclic ring is unsubstituted or substituted with 1 or 2 substituents independently selected from:

- (a) halogen selected from -F, -Cl, and -Br,
- (b) methyl,
- (c) -CF₃,
- (d) methoxy,
- (e) -OCF₃,
- (f) -CN,
- (g) =O, and
- (h) -OH; and

R^t is selected from pyrrolidinyl, pyrazolidinyl, imidazoliny, piperidinyl, piperazinyl, pyrrolyl, pyridyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, and pyradiziny; any one of which is unsubstituted or substituted with 1 or 2 substituents independently selected from -F, -Cl, -Br, oxo, methyl, and methoxy;

or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 5, which is a compound selected from a compound of Formula (IV):



or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, which is a compound selected from the group consisting of:

7-[(3-phenylpyrrolidin-1-yl)carbonyl]-1,6-naphthyridin-8-ol;

7-[(3-benzylpiperidin-1-yl)carbonyl]-1,6-naphthyridin-8-ol;

and pharmaceutically acceptable salts thereof.

5 8. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

10 9. A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1.

15 10. A method for preventing or treating infection by HIV or treating AIDS in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound according to claim 1.

SEQUENCE LISTING

<110> Neville J. Anthony
Robert P. Gomez
Jennifer J. Bennett
Steven D. Young

<120> Aza- and Polyaza-Naphthalenyl
Carboxamides Useful As HIV Integrase Inhibitors

<130> 20759Y

<150> 60/239,679

<151> 2000-10-12

<160> 2

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 1

tgaccaaggg ctaattcact

20

<210> 2

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic DNA

<400> 2

actggttccc gattaagtga

20

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number
WO 02/055079 A3

(51) International Patent Classification⁷: **A61K 31/44**,
31/495, 31/50, 31/52, 31/53, 31/519, 31/517, 31/47, A61P
31/18, C07D 215/12, 215/16, 215/38, 237/26, 237/28,
239/72, 241/36, 251/00, 257/08, 401/02, 403/00, 471/00,
487/00

(21) International Application Number: PCT/US01/42565

(22) International Filing Date: 9 October 2001 (09.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/239,679 12 October 2000 (12.10.2000) US

(71) Applicant (for all designated States except US): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ANTHONY, Neville, J.** [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **GOMEZ, Robert, P.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **BENNETT, Jennifer, J.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **YOUNG, Steven, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
6 September 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AZA-AND POLYAZA-NAPHTHALENYL CARBOXAMIDES USEFUL AS HIV INTEGRASE INHIBITORS

(57) Abstract: Aza- and polyaza-naphthalenyl carboxamide derivatives including certain quinoline carboxamide and naphthyridine carboxamide derivatives are described as inhibitors of HIV integrase and inhibitors of HIV replication. These compounds are useful in the prevention or treatment of infection by HIV and the treatment of AIDS, as compounds or pharmaceutically acceptable salts, or as ingredients in pharmaceutical compositions, optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of preventing, treating, or delaying the onset of AIDS and methods of preventing or treating infection by HIV are also described.

WO 02/055079 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/42565

A. CLASSIFICATION OF SUBJECT MATTER		
IPC(7) : A61K 31/44, 31/495, 31/50, 31/52, 31/53, 31/519, 31/517, 31/47; A61P 31/18; C07D 215/12, 215/16, 215/38, 237/26, 237/28, 239/72, 241/36, 251/00, 257/08, 401/02, 403/00, 471/00, 487/00 USCL : 514/241, 243, 245, 248, 249, 252.17, 253.04, 253.06, 264.1, 264.11, 266.2, 266.21, 266.22, 266.23, 266.24,		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) U.S. : Please See Continuation Sheet		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/16747 A1 (DAIICHI PHARMACEUTICAL, CO., LTD.) 08 April 1999, see entire document.	1, 2 and 8
X	US 6,211,376 B1 (ROMINES et al.) 03 April 2001, see entire document, especially column 223.	1, 2 and 8
X	US 4,416,884 A (ISHIKAWA et al.) 22 November 1983, see entire document, especially example 10.	1, 2 and 8
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 03 June 2002 (03.06.2002)		Date of mailing of the international search report 28 JUN 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Brenda L. Coleman Telephone No. 703-308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/42565

Continuation of B. FIELDS SEARCHED Item I:

514/241, 243, 245, 248, 249, 252.17, 253.04, 253.06, 264.1, 264.11, 266.2, 266.21, 266.22, 266.23, 266.24, 300, 312, 313, 314;
544/179, 183, 184, 212, 215, 217, 219, 235, 236, 279, 283, 284, 287, 293, 350, 353, 354, 355, 356, 362; 546/123, 153, 154, 155, 156,
159, 160, 161, 162, 163, 168